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3. blastomycetes
4. microsporum
5. trichophyton
6. pathogenic fungi
7. pathogens
8. contaminants
9. immune reactions
10. antibiotics

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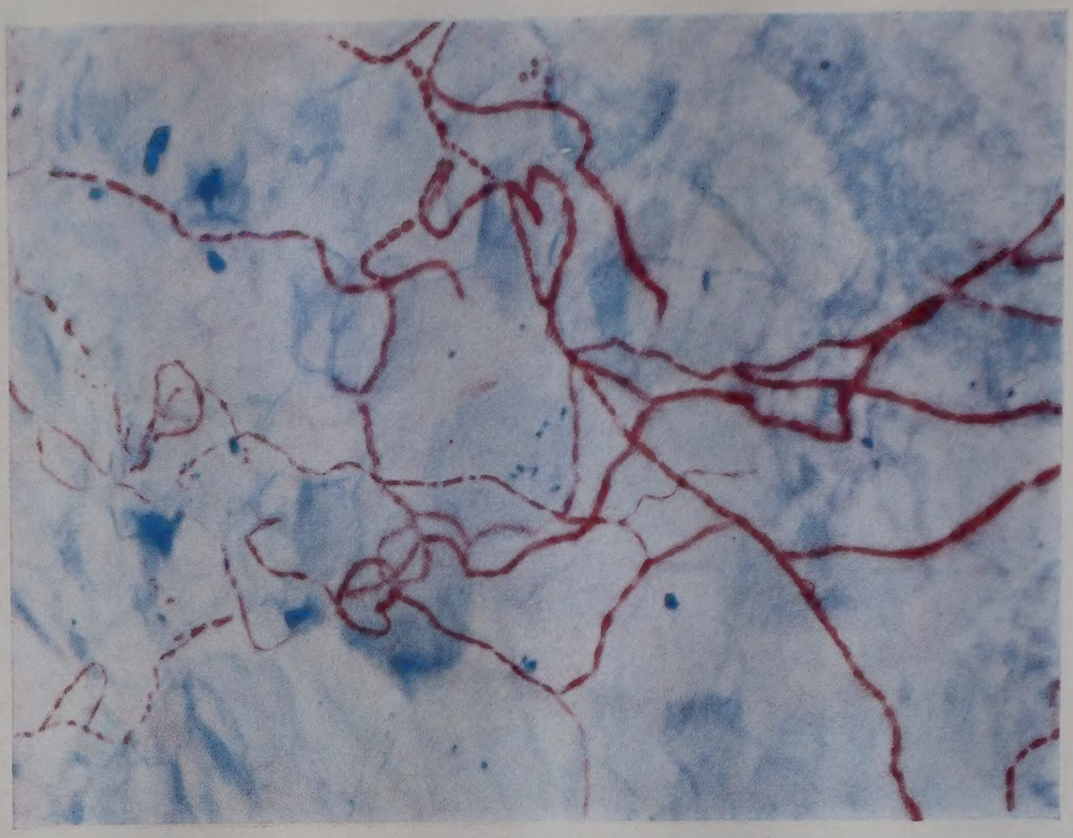
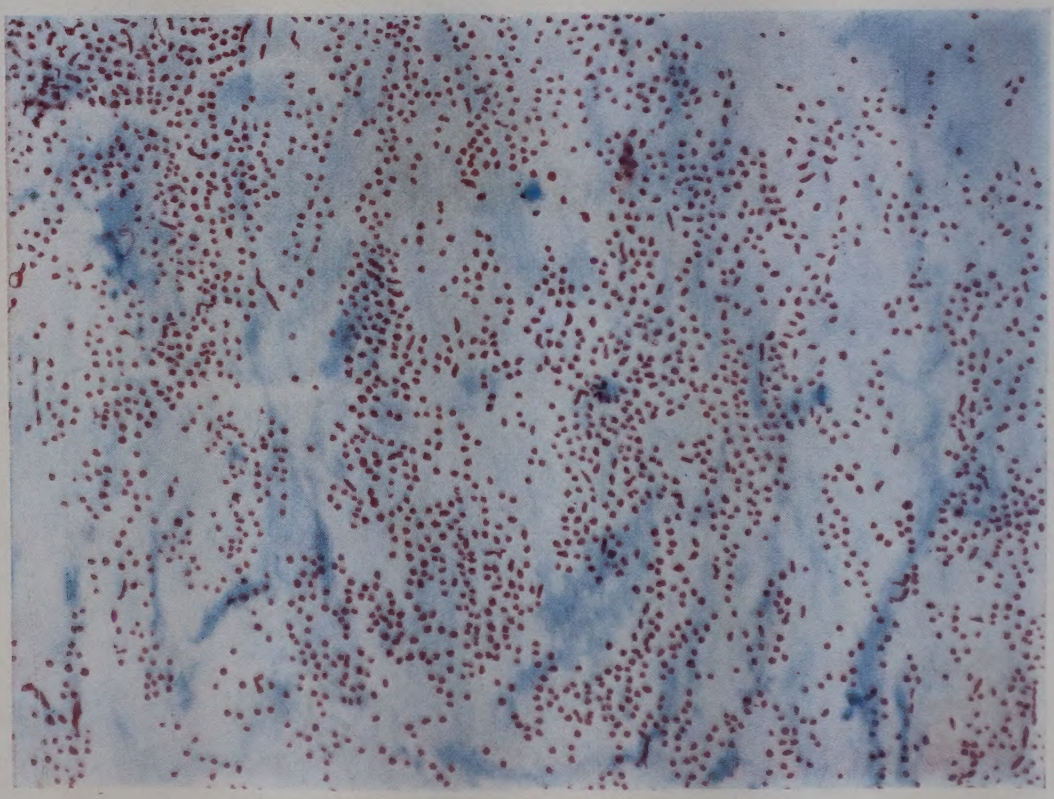
ELEMENTS OF MEDICAL MYCOLOGY





TOP: Direct microscopic examination of skin scales, showing branching septate mycelium. × 400.

BOTTOM: Infected hair, showing numerous spores. × 400

ELEMENTS OF MEDICAL MYCOLOGY

By

JACOB HYAMS SWARTZ, M.D.

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INTRODUCTION BY

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Professor of Dermatological Research, University of Pennsylvania

SECOND EDITION

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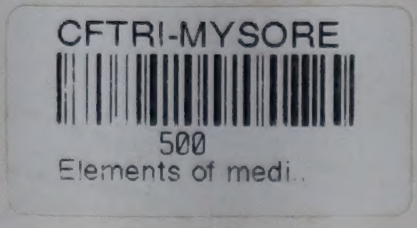

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the United States of America
Bound by Moore & Co., Inc., Baltimore
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To

MY DEAR WIFE, JANET

in evidence of my appreciation of her encouragement and self sacrifice to make this and other works possible.

INTRODUCTION TO THE FIRST EDITION

It is only within comparatively recent years that American medicine has known a text of any kind that was confined to mycology. At best, information short of general medical literature in English and texts in foreign languages could be secured only in texts on tropical medicine and, in a small way indeed, in texts on bacteriology and general medicine. However, during the last thirteen years, four texts on mycology have made their appearance—one on cutaneous mycology, one that stresses taxonomy, one emphasizing clinical mycology, and a fourth dealing with fungi from the biologic angle. None of them is encyclopedic for the whole realm of mycology, to say the least.

It is in such a setting that this book of Dr. Swartz's appears. It complements and amplifies the present supply of data, both in its text and in its illustrations.

The form that the book takes reflects the mycologic experience of its author. As a one-time pupil of Dr. Carroll W. Dodge, he follows Dodge's classification of the fungi, and has arranged his subject matter, including his chart, according to fungus genera. It is clear, too, that the laboratory aspects of mycology have become Dr. Swartz's medical hobby, as evidenced by the majority of his illustrations. As a dermatologist, he devotes special space to ringworm. As a teacher, he has properly indulged in photographs and charts; the illustrations are original, with few exceptions.

The end result is a book that should answer the plea of that type of beginner in mycology, whether student or physician, who prefers to approach disease according to the tenets of the pathologist—that is, to begin with the cause and thereafter follow the course of events into symptomatology. For those who use the clinical approach, the book will be valuable in

complementing the study of mycology through a second facet, thereby supplying the third dimension, so to speak, that could otherwise be obscured or lost by one-eyed vision.

FRED D. WEIDMAN, M.D.

Philadelphia, August, 1943

PREFACE TO THE SECOND EDITION

It is now six years since the publication of the first edition of "Elements of Medical Mycology." Since then, additional information and new technics have been advanced. A greater interest in the field of medical mycology, not only by dermatologists but also by internists and surgeons, has become manifest. The field of antibiotics and new chemotherapeutic agents has shown remarkable advances. For these reasons, then, a revised edition of this book seemed timely.

The style as presented in the first edition has been retained, despite the increase in size. Clinical aspects are discussed in greater detail and are more fully illustrated. The less common diseases caused by fungi are included. The first two chapters deal with the classification of the pathogenic fungi and diagnostic procedures. The chapters which follow discuss the micro-organisms, the tissues attacked, diseases produced, and treatment. The immune reactions and the antibiotics and newer chemotherapeutic agents are briefly reviewed.

This book is offered as a guide to students of mycology and dermatology as well as to internists and surgeons. It makes no pretense of being a complete reference book. For such purpose, the reader is referred to the painstaking and thorough work of Carroll W. Dodge.

Jacob Hyams Swartz, M.D.

Boston, April, 1949

PREFACE TO THE FIRST EDITION

This text has been designed to serve the practitioner as a guide in the study of fungus diseases. The aims of simplicity and conciseness in both content and expression have required sacrifice of a certain amount of detail and of the discussion of certain of the rarer diseases As a result, some of the statements that appear in the following pages may, to the experienced mycologist, because of the economy of detail, seem dogmatic.

If this small volume succeeds in its purpose of familiarizing students and physicians with the terminology of mycology, with the more common diseases produced by fungi, and with the laboratory procedures employed in diagnosis of these, the labor of compiling it will be sufficiently rewarded.

The book makes no pretense at serving the purposes of a definitive text. For such a work, the reader is referred to the painstakingly thorough work of Dodge, which is the foundation on which this volume has been built.

JACOB HYAMS SWARTZ, M.D.

Boston, July, 1943

ACKNOWLEDGMENTS

I am indebted to Dr. Carroll W. Dodge, whose pupil I am proud to have been. He directed my early interests and efforts in the field of medical mycology. I am also indebted to my former chief, Clarence Guy Lane, whose sound advice was freely given.

I owe a particular debt of gratitude to my collaborator, Dr. Ethel M. Rockwood, who helped with the illustrations and read the manuscript.

Dr. Norman F. Conant was generous in supplying illustrations of some of the rare fungus diseases.

Dr. Laurence L. Robbins and Dr. E. B. D. Neuhauser supplied and helped interpret the x-ray films.

My associate, Dr. Earl A. Glicklich, made my task easier by relieving me of some of the office work.

The following textbooks have been used as references in the writing of this book:

Manual of Clinical Mycology, by N. F. Conant, Ph.D., Donald S. Martin, M.D., David T. Smith, M.D., Roger D. Baker, M.D., and Jasper L. Callaway, M.D. (Philadelphia: W. B. Saunders Company, 1944)

Medical Mycology: Fungous Diseases of Men and Other Mammals, by C. W. Dodge, Ph.D. (St. Louis: C. V. Mosby Company, 1935)

An Introduction to Medical Mycology, by George M. Lewis, M.D., and Mary E. Hopper, M.S. (Chicago: Year Book Publishers, Inc., 1939)

Fungous Diseases: A Clinico-mycological Text, by Harry P. Jacobson, M.D. (Springfield, Ill.: Charles C Thomas, 1932)

Précis de parasitologie, vol. 2, by E. Brumpt (Paris: Masson et Cie, 1936)

Three Thousand Mycological Terms, by Walter H. Snell (Publication no. 2, Rhode Island Botanical Club, Providence, R.I., 1936)

Diagnosis and Treatment of Skin Diseases, by J. H. Swartz, M.D., and Margaret Gleason Reilly, R.N. (New York: Macmillan Company, 1935)

J. H. S.

HISTORICAL NOTE

Mycology, the study of fungi, came into existence before bacteriology. It began when Hooke, in 1677, constructed a magnifying lens and studied the yellow spots on the leaves of the damask rose and found that they consisted of filamentous organisms that he described in detail and illustrated with drawings.

In 1686, Malpighi devoted a chapter to "Plantis quae in aliis vegetant." In this chapter he mentions the genus Mucedo. In 1729, Michelli described the genus Aspergillus among other fungi. In 1752, Linnaeus, in his book entitled *Species plantarum*, summarized all that was known on the subject of fungi, and also named a large number of species.

A good deal of progress was made in mycology in the early part of the nineteenth century. It was not until then that fungi parasitic to man began to attract attention. The first important fungus discovered was that which causes thrush; this organism was described by Langenbeck in 1839. In 1843, Charles Robin described the thrush fungus in detail. Robin also wrote a book on mycology entitled *Histoire naturelle des végéteaux parasites qui croissent sur l'homme et sur les animaux vivants.*

In 1843, Schoenlein discovered the fungus producing favus. In that year Gruby described the fungus of ringworm, and pointed out the difference between ringworm fungi of the large-spore and of the small-spore type. In 1846, Eichstedt discovered the fungus of tinea versicolor. In 1870, Tilbury Fox described tinea pedis.

Mycology continued to attract attention up to the time of the discoveries by Pasteur and Koch in the field of bacteriology; these discoveries brought bacteriology into the foreground at the expense of mycology. However, in 1910 Sabouraud's scien-

tific work on the subject of mycology brought to the fore a neglected and almost forgotten subject; his book *Les teignes* is a classic.

Since then numerous workers both in this country and abroad have worked hard and made excellent progress on the subject of mycology. Castellani merits mention for his work on the tropical mycoses; Jadassohn and Bloch for their researches particularly in the field of immunology of fungus diseases; Mieschen, Bruhns, and Alexander for their work on dermatophytes; De Beurmann for his investigations of sporotrichosis.

Outstanding in this country are the names of Weidman, Hopkins, Benham, Williams, Dodge, Henrici, Emmons, Jacobson, Martin, Conant, Moore, Lewis, and Hopper, among the large number of workers who are continuing the researches in mycology begun in the early nineteenth century.

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CHAPTER I

GENERAL DISCUSSION

Origin and Morphology of Fungi

The fungi compose a large, heterogeneous group of plants, classified as thallophytes and characterized by their lack of chlorophyll. In contrast to the algae, which obtain their nutrition from inorganic substances with the aid of chlorophyll and the sun's energy, the fungi live on decayed organic matter. Structurally, fungi show two distinct parts, the vegetative and the reproductive portions.

VEGETATIVE PORTION

This part is called the *thallus* or *mycelium*, and is made up of septate filaments called *hyphae*. The latter are surrounded by cell walls. An exception are the few primitive families showing a naked and ameboid vegetative body. In a few groups the hyphal walls give the cellulose reaction, but most of them give the chitin reaction. In fructifications and resting cells, the hyphal wall first appears as a thin hyaline membrane that becomes thicker and may be further differentiated by secretions and deposits of minerals or resins or colored by pigments. The individual hyphae are generally intertwined in feltlike masses. Such a mass usually absorbs food at any point of the surface. Small mycelial branches that serve to attach the mycelium to the substrate and absorb the nutrients take on a specialized form and function in several groups. When the absorbing organs are rootlike, they are described as *rhizoids*. When their function is purely that of attachment, the organs are called *holdfasts* (Rhizopus).

The septum often forms by furrowing. During rapid growth, there may be a delay in this septal development, later com-

pensated by simultaneous or successive developments of septa. In some species (viz., Phycomycetes), the septa are entirely suppressed. The whole mycelium is then a single, branched multinuclear mass of filaments, becoming septate during the formation of reproductive organs or under conditions of poor nutrition.

REPRODUCTIVE PORTION

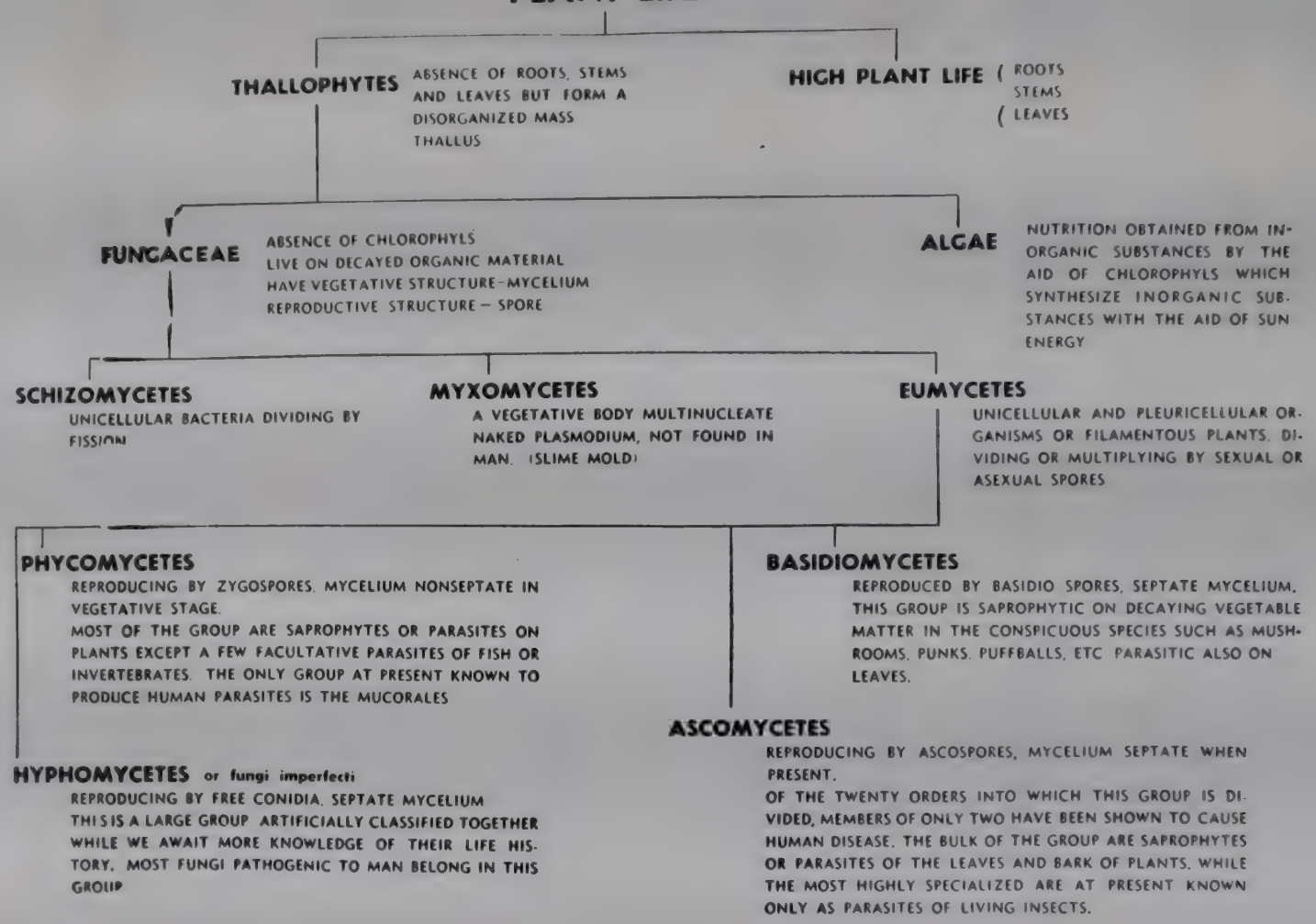
This part is made up of *spores*. Spores may be defined as characteristically formed cells or groups of cells that separate from the mother plant and take on an individual identity as new, independent structures. They serve a propagative purpose or that of resisting unfavorable environmental conditions. The simplest form of development is that in which hyphal cells separate from the parent hyphae and develop into new hyphae. These individual cells are called *arthrospores* or *thallospores*. From these there is a gradual transition to more typical spores having a characteristic form. The spores are in many cases formed by abstriction; in others, spores arise on specialized sporophores. Sporophores to which specialized sporogenous cells are attached are known as *sporangiophores*. The spores within the sporangia (specialized sporogenous cells) are termed *sporangiospores*. Conidiophores are sporophores that abjoint their spores exogenously at their tips; these spores are called *conidia*. Spores may have a sexual origin, representing the fusion of two cells, or they may be asexual. Most pathogenic fungi produce asexual spores; some of them, both sexual and asexual spores. Those producing sexual spores are called *perfect fungi;* those showing only the asexual type, *imperfect fungi*.

Physiology

GROWTH AND REPRODUCTION

Water. The fungi grow and reproduce best in relatively high humidity. This characteristic makes it possible, by trans-

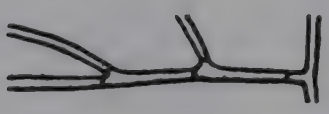
ORIGIN OF FUNGI


PLANT LIFE
THALLOPHYTES
ABSENCE OF ROOTS, STEMS AND LEAVES BUT FORM A DISORGANIZED MASS THALLUS
HIGH PLANT LIFE (ROOTS STEMS (LEAVES
FUNGACEAE
ABSENCE OF CHLOROPHYLS
LIVE ON DECAYED ORGANIC MATERIAL
HAVE VEGETATIVE STRUCTURE-MYCELIUM
REPRODUCTIVE STRUCTURE – SPORE
ALGAE
NUTRITION OBTAINED FROM INORGANIC SUBSTANCES BY THE AID OF CHLOROPHYLS WHICH SYNTHESIZE INORGANIC SUBSTANCES WITH THE AID OF SUN ENERGY
SCHIZOMYCETES
UNICELLULAR BACTERIA DIVIDING BY FISSION
MYXOMYCETES
A VEGETATIVE BODY MULTINUCLEATE NAKED PLASMODIUM, NOT FOUND IN MAN. (SLIME MOLD)
EUMYCETES
UNICELLULAR AND PLEURICELLULAR ORGANISMS OR FILAMENTOUS PLANTS, DIVIDING OR MULTIPLYING BY SEXUAL OR ASEXUAL SPORES
PHYCOMYCETES
REPRODUCING BY ZYGOSPORES. MYCELIUM NONSEPTATE IN VEGETATIVE STAGE.
MOST OF THE GROUP ARE SAPROPHYTES OR PARASITES ON PLANTS EXCEPT A FEW FACULTATIVE PARASITES OF FISH OR INVERTEBRATES. THE ONLY GROUP AT PRESENT KNOWN TO PRODUCE HUMAN PARASITES IS THE MUCORALES
BASIDIOMYCETES
REPRODUCED BY BASIDIO SPORES, SEPTATE MYCELIUM. THIS GROUP IS SAPROPHYTIC ON DECAYING VEGETABLE MATTER IN THE CONSPICUOUS SPECIES SUCH AS MUSHROOMS, PUNKS, PUFFBALLS, ETC PARASITIC ALSO ON LEAVES.
ASCOMYCETES
REPRODUCING BY ASCOSPORES, MYCELIUM SEPTATE WHEN PRESENT.
OF THE TWENTY ORDERS INTO WHICH THIS GROUP IS DIVIDED, MEMBERS OF ONLY TWO HAVE BEEN SHOWN TO CAUSE HUMAN DISEASE. THE BULK OF THE GROUP ARE SAPROPHYTES OR PARASITES OF THE LEAVES AND BARK OF PLANTS, WHILE THE MOST HIGHLY SPECIALIZED ARE AT PRESENT KNOWN ONLY AS PARASITES OF LIVING INSECTS.
HYPHOMYCETES or fungi imperfecti
REPRODUCING BY FREE CONIDIA, SEPTATE MYCELIUM
THIS IS A LARGE GROUP ARTIFICIALLY CLASSIFIED TOGETHER WHILE WE AWAIT MORE KNOWLEDGE OF THEIR LIFE HISTORY. MOST FUNGI PATHOGENIC TO MAN BELONG IN THIS GROUP

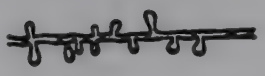
DEFINITIONS

THALLUS. The entire vegetative portion of the fungus.

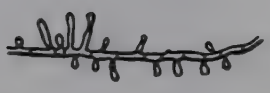
HYPHA. A chain of cylindric or club-shaped cells forming a filament.



MYCELIUM. A mass or collection of hyphae.

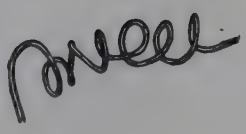


SPOROPHORE. A specialized hypha to which spores are attached.



STERIGMA. A specialized hyphal cell to which spores are attached.

CLUBS. Swollen hyphal tips, varying greatly in size.

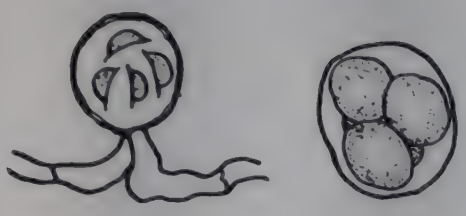


SPIRALS. Simple convoluted hyphae that may take all the forms of a tendril—from a spirillum-like form to a closely set coil.

RACQUET MYCELIUM. Club-shaped cells, the clubbed end of one cell being attached to the small end of an adjacent cell.

CHLAMYDOSPORES. Thallospores formed by the concentration of the protoplasm of a hypha within a swollen portion of the filament, the membrane of which becomes thickened. They are purely resting spores and are closely analogous in function to the spores of bacteria.

FUSEAUX. Large elongated chambered bodies looking very much like chlamydospores and divided into segments by parallel transverse septa.

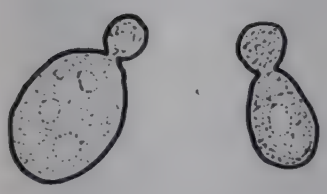


ENDOSPORE. Any spore formed within a membrane of the parent cell.

ASCOSPORES. A special class of endospores formed in a membrane known as the ascus. The number of spores in the sac is limited to two, four, or eight, and is constant for the particular species producing them.

BASIDIOSPORE. An exospore on a special type of sporophore known as a basidium.

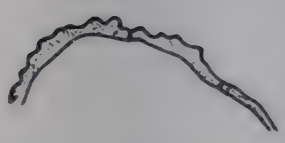
THALLOSPORE. Cells that form a part of the vegetative portion of the fungus.



BLASTOSPORE. A thallospore that develops by budding from the end or side of the parent cell and that may in turn throw out another bud or a mycelial filament, without becoming detached, and without any period of latency. The buds of yeast cells are familiar examples.

ARTHROSPORES. Structures formed by the segmentation of a hypha into a chain of cells, at first cubical and later rounded.

CONIDIA. Cells of irregular shape and size, borne free and originating asexually from the mycelial threads by a process of budding, septation, or abstriction. They may be pedunculated, nonpedunculated, lateral, or terminal.



PECTINATE BODIES. Swollen and frequently curved ends of hyphae that give off a row of abortive branches from one side, the structure vaguely resembling a comb.

NODULAR BODIES. Large rounded cells knotted together, forming dense masses.

ZYGOSPORE. A sexual cell produced by the fusion of two undifferentiated cells.

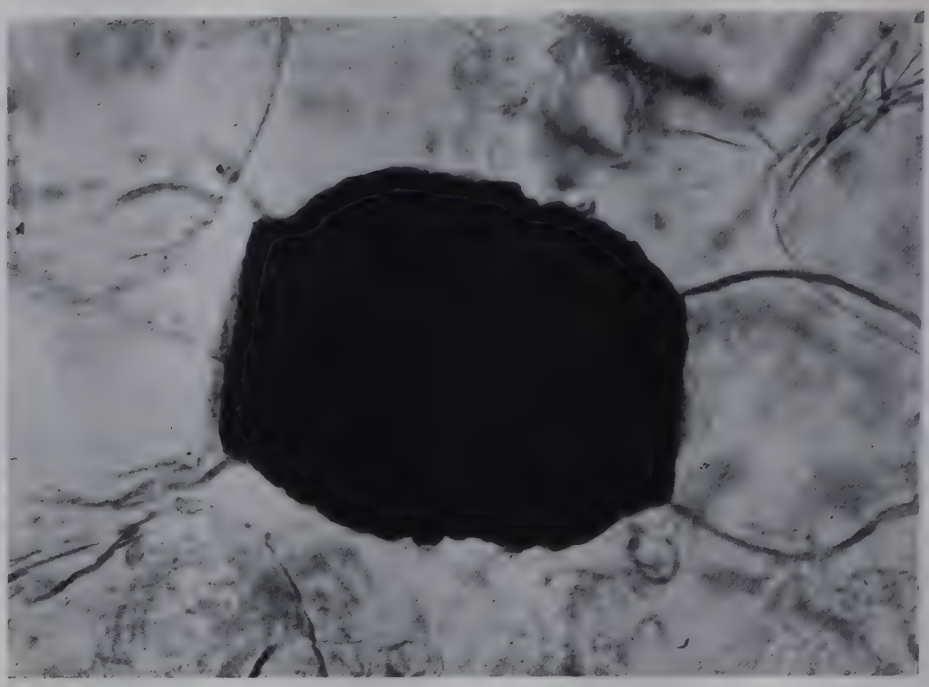


FIG. 1. ZYGOSPORE. FUSION OF TWO UNDIFFERENTIATED CELLS

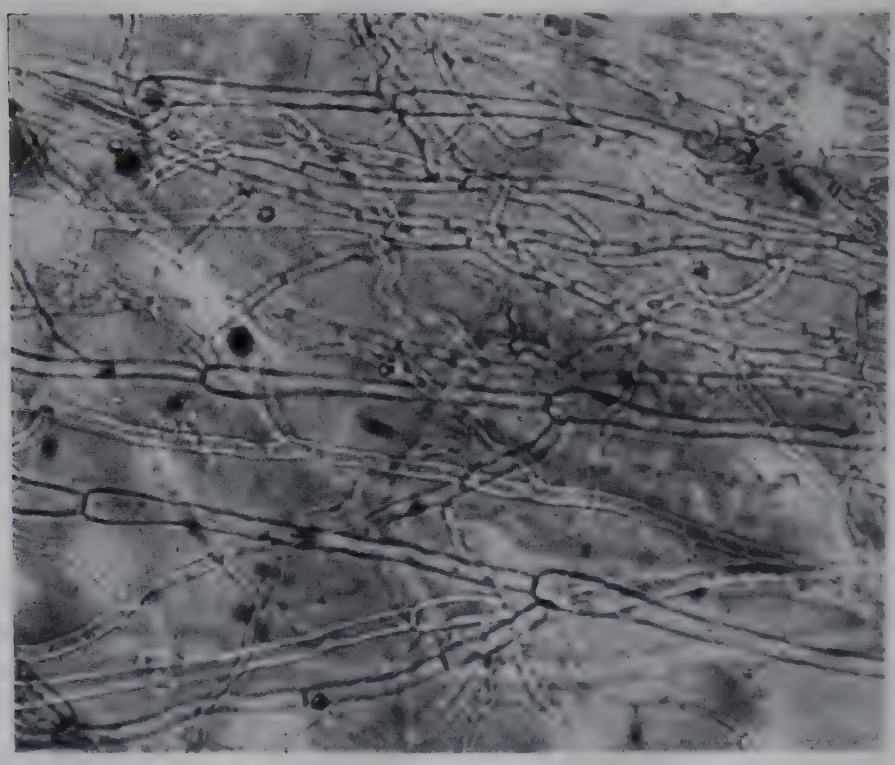


FIG. 2. RACQUET MYCELIUM

ferring, in stock cultures, to a 4 to 5 per cent agar instead of the 1.5 to 3 per cent commonly employed, to allow a much longer interval between transfers.

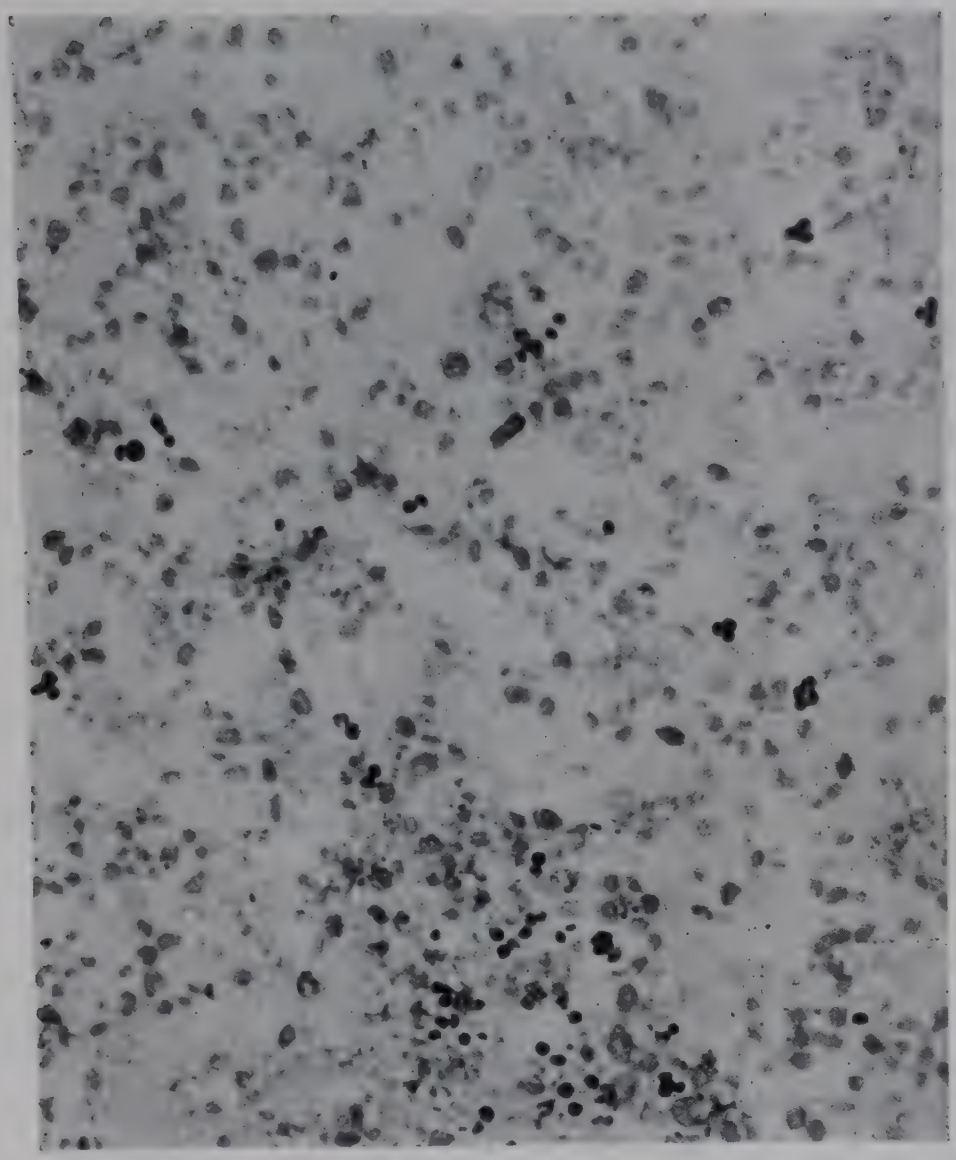


FIG. 3. ASCOSPORES

Oxygen. The common pathogenic fungi require oxygen for growth and reproduction. Actinomyces bovis, however, is an exception.

Nitrogen. The usual source of nitrogen in culture media is peptone. In the skin, keratin is the source of nitrogen. The manner in which the skin fungi utilize the amino acids in keratin has not been determined. It has been shown that most fungi require amino acids when grown on artificial media and that a suitable mixture of amino acids is desirable for the optimum growth and reproduction.

Inorganic Salts. Traces of potassium, magnesium, iron, and calcium are necessary to secure good growth and reproduction. Of the nonmetallic elements, phosphorus, sulfur, carbon, and nitrogen are important.

Hydrogen Ion Concentration. Most fungi grow best in media supplying a concentration between *p*H 5 and *p*H 7.

Temperature. Optimum temperatures vary greatly with the species. Some species grow well only at body temperature, others at any level between room and body temperature. Most pathogenic fungi grow well at room temperature.

Light. Most pathogenic fungi develop as well in the dark as in light. Ultraviolet rays of special wave lengths do have an inhibiting influence. Roentgen rays have proved to have only slight inhibiting influence.

Pigment. Lewis and Hopper, in their study on the production of pigment, concluded that pigment is the product of metabolism. Trichophyton rubrum and Microsporum canis were found to synthesize pigment in the presence of such monosaccharides as dextrose, levulose and mannose and one disaccharide, mannitol. Pigment was not produced when the only sugars in the culture medium were disaccharides, trisaccharides, polysaccharides and one monosaccharide, galactose. Foster stresses the importance of available minerals particularly iron, copper, and manganese.

Classification of Pathogenic Fungi

The pathogenic fung may be classified as follows:

I. Yeast and yeastlike fungi
   - A. Perfect
     1. Saccharomycetaceae (true yeast)
     2. Endomyces (auct.) (filamentous yeast)
   - B. Imperfect
     1. Cryptococcus (Torula)
     2. Candida (Monilia)
     3. Pityrosporum

II. Ringworm fungi
    1. Microsporum
    2. Trichophyton
    3. Epidermophyton
    4. Endodermophyton
III. Other pathogenic imperfect fungi
    1. Coccidioides immitis
    2. Paracoccidioides brasiliensis
    3. Hormodendrum
    4. Histoplasma capsulatum
    5. Malassezia furfur (Microsporum furfur)
    6. Microsporum minutissimum (Actinomyces minutissimus)
    7. Sporotrichum
    8. Actinomyces
    9. Blastomyces dermatitidis

The pathogenic fungi may also be classified as follows:

I. The Superficial
    1. Microsporum
    2. Trichophyton
    3. Epidermophyton
    4. Malassezia furfur (Microsporum furfur)
    5. Actinomyces minutissimus (Microsporum minutissimum)
    6. Hormodendrum
    7. Cryptococcus (Torula)
    8. Candida (Monilia)

With the exception of Cryptococcus and Candida the fungi listed above are not known to attack the visceral organs although dissemination by the blood stream may occur.

II. The Deep: These micro-organisms may attack visceral organs. The skin may be of primary or secondary involvement.
    1. Actinomyces

2. Coccidioides immitis
3. Paracoccidioides brasiliensis
4. Blastomyces dermatitidis
5. Sporotrichum schenki
6. Histoplasma capsulatum
7. Cryptococcus neoformans
8. Candida albicans
9. Rhinosporidium seeberi
10. Aspergillus
11. Geotrichum

Fungi and Their Relation to Disease

The following is a classification of the pathogenic fungi, the tissues attacked by each, and the diseases they produce.

Cryptococcus (*Torula*)
Nervous system: meningitis
Skin: cryptococcosis epidermica
European blastomycosis

Candida (*Monilia*)
Mucous membrane: thrush
vaginitis
Skin: moniliasis. Folds, and interdigital areas on the hands are particularly susceptible
chronic paronychia
Lungs: broncho-pulmonary moniliasis
Systemic involvement: positive blood cultures

Microsporum
M. Canis (*lanosum*): animal type
Most frequently, in this country, tinea capitis in children; occasionally, tinea barbae. May involve glabrous skin in both children and adults
M. audouini; human type
Tinea capitis in children. Rarely, attacks glabrous skin, producing abortive lesions. More frequently found in England

M. Gypseum (*fulvum*): animal type
Tinea capitis and glabrous skin involvement in children
Trichophyton schoenleini (*Achorion schoenleini*)
Scalp, body, and nails: favus
Trichophyton gypseum
Kerion
Tinea sycosis
Glabrous skin involvement
Trichophyton rubrum
Extensive glabrous skin involvement
Onychomycosis
Trichophyton rosaceum
Tinea sycosis
Onychomycosis
Trichophyton violaceum
Tinea capitis (black dot ringworm)
Kerion
Tinea sycosis
Glabrous skin involvement
Trichophyton tonsurans (*T. crateriforme*)
Tinea capitis
Trichophyton sabouraudi (*T. acuminatum*)
Tinea capitis
Trichophyton sulfureum
Tinea sycosis
Tinea capitis
Glabrous skin involvement
Epidermophyton floccosum (*E. inguinale*)
Hands, feet, groins: fungus infection (viz., dermatophytosis, also caused by Trichophyton family)
Endodermophyton (*E. concentricum*) (*T. concentricum*)
Skin: Tokelau ringworm (tinea imbricata). Occurs in China, the Malay Peninsula, various Pacific islands
Malassezia furfur (*Microsporum furfur*)
Skin, particularly upper trunk and extremities: tinea versicolor

Actinomyces minutissimus (*Microsporum minutissimum*)
Skin particularly groins and axillae: erythrasma

Hormodendrum
Philalophora verrucosa
Skin: chromblastomycosis

Rhinosporidium seeberi
Anterior nares: rhinosporidiosis

Blastomyces dermatitidis
Skin, deep structures, lungs, central nervous system (rarely): American blastomycosis

Sporotrichum (S. schencki)
Skin, systemic involvement: sporotrichosis

Coccidioides immitis
Tissues of the pulmonary, osseous, cerebrospinal, and cutaneous systems, these appearing to bear the brunt of the infection (with the exception of the gastro-intestinal tract, no part of the body is entirely immune): coccidioidomycosis (California disease), two forms—acute (valley fever) and granulomatous. Endemic in certain parts of North America; sometimes benign, usually malignant and rapidly fatal. Clinically simulates tuberculosis, syphilis, glanders, or neoplasm

Paracoccidioides brasiliensis
Skin, mucous membrane and visceral organs: de Almeida's disease; Lutz's disease; granuloma paracoccidioides

Actinomyces (Nocardia bovix, N. israeli)
Skin (particularly of head and neck), systemic involvement: actinomycosis

Histoplasma capsulatum
Skin: histoplasmosis (Darling's disease). Systemic: (Reticuloendothelial-cytomycosis)

Aspergillus (*A. fumigatus; A. niger*)
Skin, nails and lungs: aspergillosis

Geotrichum-Link
Oral mucous membranes: Broncho-pulmonary geotrichosis

CHAPTER II

DIAGNOSIS OF FUNGUS INFECTION

THE DIAGNOSIS of fungus infection is made on the basis of the clinical picture. It can be confirmed by the following laboratory procedures:

1. Direct microscopic examination
2. Cultural characteristics
   a) culture media
   b) gross appearance
   c) microscopic appearance
   d) fusion of mycelium
   e) fermentation test
3. Filtered ultraviolet radiation
4. Cutaneous test
5. Animal inoculation
6. Agglutination test
7. Precipitation and complement fixation tests
8. Histologic examination
9. Roentgenologic examination

DIRECT MICROSCOPIC EXAMINATION

MATERIAL

A microscopic examination of the suspected material is requisite in every case diagnosed as fungus infection. The selection of proper material is important, since hit-or-miss selection accounts for many negative findings. It is wise, also, to take plenty of material for both culture and direct microscopic study.

In tinea capitis, the stumps of hairs make the best material; in tinea barbae, both the involved hairs and the contents of the abscesses are used. In tinea of the glabrous skin (viz.,

tinea cruris, tinea circinata, or dermatophytosis of the hands or feet), the skin scrapings must be taken from the margins and rolled toward the normal skin, or from the roofs of the vesicles. In blastomycosis, we look for double-contoured bodies in the pus; they may also be seen in tissue in or outside the giant cells. In actinomycosis, the sulfur granules in the discharge are the best material for study. If mycosis of the lungs is suspected, a specimen of the sputum or preferably fragment of tissue or secretion obtained by bronchoscopic examination should be used for direct microscopic examination and cultural studies.

APPARATUS

The essential equipment for direct microscopic examination of the material in question comprises the following:

1. Epilating forceps for removal of hairs
2. Small curette or epilating forceps for glabrous skin
3. Sharp-pointed toothpick to help in transferring the scales from the forceps or curette to the slide
4. Several glass slides and a cover glass, thoroughly cleansed with alcohol
5. Tuberculin syringe and 20 gage needle to aspirate pus
6. Scalpel to cut up coarse scales and nails
7. Small curette for obtaining nail material
8. Ten per cent solution of cresol for sterilizing curettes and scalpels

TECHNIC

Place the material on a slide, adding a few drops of 20 to 40 per cent sodium or potassium hydroxide, preferably the latter. Cover with a cover glass, heat slightly, and allow to clear for ten or fifteen minutes before examining under the microscope. Do not mistake fat globules or air bubbles for spores. Do not mistake potassium hydroxide crystals for branching mycelia. Do not use too much potassium hydroxide in preparing the

slide; it will run over the cover glass and the preparation will be messy and unsatisfactory.

Do not boil the potassium hydroxide when warming the slide.

Do not rely on a single negative microscopic finding. Examine at least three preparations.

Stains for Hair and Scales. Staining is necessary for permanent preparation, since potassium hydroxide in a few days or even hours destroys the mycelium and the outline of the spores. Of the staining procedures described in the literature, the following deserve especial mention.

Adamson (1895) recommended clearing with 5 to 10 per cent potassium hydroxide and staining by the Gram method. Chalmers and Marshall (1914) suggested soaking scales for some hours in 40 per cent potassium hydroxide placed on a watch glass in the incubator at 40 C., then transferring the specimens to watch glass containing 15 per cent alcohol. After thirty minutes they should be removed to a slide, the alcohol being allowed to evaporate. After drying over a flame, the specimens are stained with aniline gentian violet over a thirty-minute period. They are then treated for three minutes with Gram's iodine solution, decolorized for thirty minutes with aniline oil, and stained for a minute in concentrated alcoholic eosin, which is then washed off with aniline oil or clove oil. Finally, the specimens are treated with xylol and mounted in balsam.

Unna's method (1891) is to rub the scales of the epidermis between two slides in a little glacial acetic acid. The slides are then drawn apart and held briefly over a flame to dry. With alcohol and ether the fat is removed, and the preparations are stained in borax–methylene blue.

Unna, Jr. (1929), recommends the following modification of the Pappenheim-Unna, Sr., method. Fix the skin in absolute alcohol, run it through alcohol to xylol, and embed it in paraffin. Cut 10-microns-thick sections of the skin, stain them with pyronine–methyl green for five to ten seconds, rinse in water,

dry with absolute alcohol, and mount in balsam. The fungi are stained red, and the leukocytes green to blue-green.

The Swartz-Conant* stain has the advantage of (1) giving a permanent preparation for class demonstration, and (2) eliminating artefacts that might be mistaken for fungi. The technic is as follows: The cutaneous scales, nail scrapings, or hairs are given preliminary clearing with a 5 to 10 per cent solution of potassium hydroxide and transferred to a watch glass. Two or three minutes of washing with water will stop the action of the potassium hydroxide, and the material is then transferred to a slide and gently heated in a drop of lactophenol–cotton blue and a cover glass pressed on the preparation. The epidermal cells are stained light blue, the granular protoplasmic content of the fungus a deep blue. The stained material may be mounted in clear lactophenol.†

Williams (1927) recommends the use of glycerin to replace the potassium hydroxide after the skin scale is treated with the latter (see p. 14). Such a preparation can last several months.

Stain for Sputum and Pus. The suspected sputum, pus, or exudate is put on a slide and 20 to 40 per cent potassium hydroxide is added. A cover glass is then placed over the mixture, which is heated slightly, allowed to clear, and examined microscopically under high-dry power for mycelium or spores. If

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	Gm. or cc.
*Lactic acid	1.0
Phenol crystals	1.0
Glycerin	2.0
Water (distilled)	1.0
Cotton blue (C 4B Poirrier)	0.025

The last ingredient is added after the other ingredients have been dissolved with gentle warming.

† Langeron's *Précis de microscopie* gives this formula for lactophenol:

	Gm. or cc.
Lactic acid	1.0
Phenol crystals	1.0
Glycerin	2.0
Water (distilled)	1.0

fistulas, draining sinuses, or abscesses are present, the material in order to avoid contaminants, must be obtained from fresh lesions. Sometimes several preparations must be examined before the organism is found. The lactophenol–cotton blue stain is the most satisfactory, since it does away with some of the artefacts so easy to mistake for fungi.

Wet India Ink Preparation. This procedure is useful in demonstrating the capsule in Cryptococcus neoformans. Weidman and Freeman described the technic as follows: "A loopful of india ink is placed on a glass slide and a loopful of culture material is quickly emulsified in it. A large cover slip is quickly applied and pressed gently."

Contrast Stain. This is a new method described by one of the authors (J. H. S.). The suspected material is cleared in 10 per cent potassium hydroxide until it has a semitransparency and a gelatinous consistency. This may be done in a watch glass or under a cover slip on a slide. The potassium hydroxide is then thoroughly washed out of the material with tap water using a fine pointed pipette. The material is then further cleared by soaking in a lactophenol mixture (see p. 16) until it becomes transparent. It is then placed on a clean slide and the lactophenol is washed away with tap water. If the material is rather thick, it may be smeared gently by touching the top with the flat side of a cover slip, then allowed to dry, and passed through a flame three or four times and heat fixed. If the skin scales do not dry easily the reverse side of the slide should be heated gently until the scales can be seen to adhere to the slide before heat fixing. Phloxine B (5 per cent) is applied with a medicine dropper and heated gently over a flame for thirty to sixty seconds. The slide is then washed well with tap water and blotted dry. A few drops of the supernatant fluid of a lactophenol–cotton blue* and clove oil mixture equal

* Lactophenol–cotton blue and clove oil in equal parts are mixed well in a test tube. The clear supernatant fluid is drawn off with a capillary pipette. Fresh preparation should be made weekly.

parts, is applied to the smear and heated gently over the flame. The tissue will stain light blue and the fungus will be stained red.

The major artefacts are fat cells, potassium hydroxide branching crystals, and mosaic structures—the latter irregular-shaped motheaten-like forms similating mycelium, found in the intercellular spaces. Most mycologists agree that these structures are not fungus mycelia, but disagree as to whether they are degenerated fungi, cholesterol intercellular artefacts, or a result of action of fungi on the metabolism of the epidermal cells.

Cultural Characteristics

CULTURE MEDIA

Broadly speaking, media are either solid or liquid. Solid media are the most widely used, except in certain physiologic and spore germination studies, where liquids are more useful. Tap water, milk, and similar natural liquids used alone or in combination with one or more other substances were the most popular early media. There have since come into use certain solutions of known chemical content that provide the various metallic elements necessary for growth, as well as one or more organic compounds containing the requisite carbon and nitrogen, such as the Czapek or Dox solution. The former is:

	Gm. or cc.
Distilled water	1,000.0
K_2HPO_4	1.0
KCl	0.5
$MgSO_47H_2O$	0.5
$FeSO_4$	0.01

There are in common use many formulas for both solid and liquid media containing aqueous extracts in the form of infusions or decoctions. Infusions are prepared by extracting the material, rather finely divided, and steeping it for an hour or more in water. The only one in use at present is the meat in-

fusion. A mixture of one part of finely chopped lean meat is macerated with two parts of distilled water and chilled for eighteen hours, with occasional stirring. It is then strained while cold through a fine cloth and 1 per cent peptone and 0.5 per cent sodium chloride are added. After heating of the preparation until solution is complete, sodium hydroxide is added until the reaction is slightly alkaline (practically neutral to phenolphthalein). After heating on a water bath for thirty minutes over a free flame, the mixture is filtered while still hot through paper or through cotton and cloth. Finally one per cent of the desired nutrients is added and reaction adjusted as necessary.

Because of greater speed of the process and low protein content, vegetable decoctions make suitable media. Duggar (1909) suggested the equivalent of 50 Gm. dry weight of the substance for every 1,000 cc. of water. The plant should be washed, peeled, and sliced thin. The proper amount of water is then added and the whole boiled in a steam sterilizer for two hours, never being allowed to cook on the bottom of the container. Water lost by evaporation must be replaced. After the larger vegetable particles have been removed by straining, the decoction is filtered through paper.

The earliest types of solid media were slices or plugs of raw or cooked vegetables. Raw vegetable must have the outer skin washed and sterilized, either with alcohol allowed to evaporate or with sterile water washes. Another requirement is a relatively dust- and spore-free atmosphere. Cylinders of the vegetable, cut out with a sterile cork bore of slightly smaller diameter than the test tube used, are sliced diagonally and placed either in a special sterile test tube or in one containing one or two glass beads and a small amount of water. To insure continued moisture of the surface of the slant, glycerol is sometimes substituted for the water or used in addition to it. It is well to keep in mind that the glycerol is a possible additional source of carbon.

The other solid media are colloidal gels—either silicates, proteins, or carbohydrates. The silicates, because they are difficult to prepare, are not practical. The principal proteins are egg albumin and gelatin; they are little used in mycology except in studies of the organism's ability to attack and digest protein. The carbohydrate media, chiefly starches and agar, are the most frequently used.

The most commonly used formulas for culture media are:

Sabouraud's Medium

	Gm. or cc.
Maltose (*brute de Chanut*)	40.0
Peptone (*granulèe de Chassaing*)	10.0
Agar-agar	18.0
Distilled water	1,000.0

The mixture is dissolved in the autoclave, filtered through paper, poured into Erlenmeyer flasks to a depth of about 1 cm., and sterilized once in the autoclave, allowing the temperature to rise slowly to 120 C.

The formula for Sabouraud's conservation agar is the same as that given above, except for omission of the sugar. This medium was first advocated by Sabouraud to prevent pleomorphism (the loss of cultural characteristics through excessive vegetative growth).

Conservation Agar Medium

	Gm. or cc.
Peptone	10.0
Agar-agar	18.0
Distilled water	1,000.0

Weidman's Modification of Sabouraud's Medium

	Gm. or cc.
Agar-agar	18.0
Peptone (Fairchild)	10.0
Dextrose (American granular)	40.0
Water	1,000.0

1. Dissolve ingredients and filter through cheesecloth
2. Adjustment of *p*H is not necessary (the finished medium should have a *p*H of 5.0)

3. Sterilize at 100 C. for thirty minutes on each of three successive days

CORN MEAL AGAR MEDIUM

	Gm. or cc.
Yellow corn meal	40.0
Agar-agar	15.0
Distilled water	1,000.0

Mix the corn meal with 500 cc. of water and keep heated to 65 C. for one hour. Then filter the mixture. Dissolve agar in 500 cc. water and mix the corn meal and the agar. Filter through cotton while the flask is kept in a steam bath. Fill test tubes with the desired amounts; autoclave for 20 minutes at 15 pounds pressure, slant tubes, and cool long enough to solidify the medium.

This medium particularly facilitates the differentiation of the various species of Candida (Monilia). Its chief value is to facilitate the study of characteristic spore formation. It may be used in the study of spore formation in Cryptococcus and in some of the dermatophytes.

Excellent results have frequently been reported with various fungi on carrot agar. The following is a typical formula:

FALCHI'S CARROT AGAR MEDIUM

	Gm. or cc.
Carrots	500.0
Peptone (Rostock)	10.0
Agar-agar	20.0
Water	1,000.0

POTATO-CARROT AGAR MEDIUM

	Gm. or cc.
Carrots	20.0
Potatoes	20.0
Agar-agar	15.0
Distilled water	1,000.0

Wash and peel the vegetables, cut into small pieces, add 700 cc. of water, and boil the mixture until 500 cc. remains. Filter. Dissolve the agar in 500 cc. of water by heating and mix the agar and the vegetable mixture. Put a measured amount in each test tube, autoclave, and slant.

This medium is useful to demonstrate the pigment formation characteristic for the species.

Widely used are the Currie (1917) and the Fulmer and Grimes (1923) formulas for synthetic media:

	Gm. or cc.
Ammonium chloride	1.88
Dipotassium hydrogen phosphate	1.00
Calcium chloride	1.00
Sucrose	50.00
Agar-agar	15.00
Water	1,000.00

Wort Agar (Difco)

This medium is useful for the isolation and differentiation of the yeast and yeastlike organisms. The *p*H of the medium is about 4.8 and therefore inhibits the growth of bacterial contaminants.

Anaerobic Medium (Brewer)*

* This medium is obtained from Baltimore Biological Laboratory, Baltimore, Maryland.

	Gm. or cc.
Pork infusion solids	1.0
Peptone (thio)	1.0
Sodium chloride	0.5
Sodium thioglycolate	0.1
Agar-agar	0.05
Water, qs. ad	1,000.0

Anaerobic Medium (Norris)

	Gm. or cc.
Soluble starch	2.0
Dipotassium hydrogen phosphate	0.2
Calcium chloride	0.05
Ferric chloride	0.01
Sodium nitrate	0.06
Asparagin	0.05
Agar-agar	20.0
Water, qs. ad	1,000.0

The above two media are chiefly used to isolate Actinomyces.

Bits of skin, nail clippings, horn, feathers, hair, and bone are not uncommonly employed as media in investigative work.

Thorough cleansing and sterilization of all apparatus used in work with pure culture are essential. Sterilization by chemical agents is accomplished by the use of (1) halogens—chlorine or iodine; (2) salts and heavy metals—copper, mercury, silver, etc.; (3) organic compounds—formaldehyde, phenol, salicylic compounds, and volatile oils. Sterilization by the use of such physical agents as heat and light is also possible. The autoclave is the most effective means. For most media, 10 to 20 pounds of pressure for a fifteen- to twenty-minute period is sufficient.

Filtration. To retain in proper condition biologic products easily altered by heat, it is often necessary to filter them through a porcelain filter with pores so small that bacteria cannot pass through.

The methods employed in isolation of micro-organisms are the following:

1. *Culturing of Material Taken Directly from Lesions* (see pp. 13–14).

2. *Simple Transfer.* The technic is the same as that used in bacteriology. This method is successful only when the colony is small and free of other organisms. If slight contamination is present, careful transfer from the colony under investigation may give a pure culture. Otherwise dilution and plating out must be resorted to.

3. *Dilution.* About three agar tubes are melted and then cooled almost to the solidifying point. The tube is inoculated, held vertically, and rotated to mix the contents thoroughly. A tiny drop of the melted medium is transferred to the second tube and the process is repeated several times, until three tubes have been inoculated. The contents of each tube are then poured into a Petri dish. When solidified, they are incubated until growth is evident. Individual colonies are then transferred to slants.

PRESERVATION OF FUNGI

Lewis and Hopper recommend the following method of preserving fungus colonies for demonstration purposes. When a colony has reached the size of growth desired and a characteristic appearance, the cotton pledget is moistened with a 40 per cent solution of formaldehyde and replaced in the test tube. After twenty-four hours the pledget is trimmed off even with the test tube and dipped in paraffin to prevent evaporation of moisture from the agar.

Gross cultures are studied for (1) rate of growth; (2) type of growth, i.e., smooth, granular, cottony, etc.; (3) pigment formation; (4) tendency to pleomorphism; (5) appearance of growth under a low-power microscope.

MICROSCOPIC APPEARANCE

The morphology of the organism is studied by taking a small amount of the growth, together with a little of the culture medium, staining the preparation with lactophenol–cotton blue after it is placed on a slide, and examining it microscopically. Examination is repeated at progressive stages of development. Another method of examining an organism microscopically is the van Tieghem cell technic.

Hanging-Drop Preparation (van Tieghem Cell). This is the method by which the morphology is studied while the colony is still growing. A glass ring is cemented to a microscopic slide with wax (the latter made by melting pure beeswax and vaseline), and its top is coated with vaseline. A drop of the culture medium or of water is placed in the bottom of the cell thus formed in order to produce a small moist chamber. Another, smaller drop of water or medium is placed on a clean cover glass of sufficient diameter to cover the ring. The inoculum is then placed in the center of this drop, the whole seized by forceps, and quickly inverted and lowered to the glass ring, where it is pressed down gently until the soft vaseline seals the ring. The cell may be placed on the stage of the microscope and the morphology studied from time to time.

BINDING AGENTS

For permanent preparations it is essential to use binding agents. The following are recommended.

1. Duco cement
2. Clarite
3. Asphalt varnish
4. Polyvinyl alcohol. Lactophenol–cotton blue stain may be mixed with the polyvinyl alcohol and thus have a combination clearing agent, stain and binding agent.
5. Noyer cement. Mix resin, 80 parts, with lanolin, 20 parts. Heat till thoroughly mixed. To use it heat a heavy wire, dip in the cement, and streak along the edge of the cover slip. It is necessary to work fast, since the cement hardens quickly. It may be necessary to heat the wire several times to smooth the cement along the edge of the cover slip.

FUSION OF MYCELIUM

Davidson and his co-workers have used this test to identify unknown species. Their findings show that the mycelium of strains of the same species only will fuse when allowed to mingle. The mycelium of two strains of Microsporum canis fuse, for example, while the mycelia of M. canis and M. audouini do not.

FERMENTATION TEST

Hopkins, Benham, Castellani, and others classify the yeasts and yeastlike fungi according to their fermentation reactions.

Filtered Ultraviolet Radiation

The phenomenon of fluorescence may facilitate diagnosis in cases of tinea capitis, tinea favosa, and tinea versicolor. It is a particularly valuable precautionary measure in cases in which a few infected hairs may have been overlooked in a patient about to be discharged as cured of his disease. One must, however, guard against being deceived by the fluorescence produced by greases not removed from the scalp before examination.

PROCEDURE

A Wood filter is attached to the window of an air-cooled or water-cooled quartz light radiating ultraviolet rays; photographers' black cloth is used to shut out light around the filter. The room is darkened and the rays directed at the questionable patches on the scalp or trunk. Lewis reports successful use of these rays in identifying certain organisms in cultures.

Cutaneous Test

The trichophytin test is specific but not always diagnostic. The reasons are two: (1) not every patient with a fungus infection is sensitized; the virulent fungi, for example, may not have the capacity to sensitize; (2) a positive test may denote sensitization caused by a past infection and may bear no relationship to the clinical picture in question. By and large, the test is of questionable diagnostic value.

Animal Inoculation

Inoculation of the fungus under investigation into susceptible laboratory animals may help to establish the pathogenicity of the organism. It is also valuable in obtaining a pure strain of the fungus. Animal inoculation is particularly useful in the study of the deep mycoses and of systemic infection. For animal susceptibility, refer to chart at the end of the book.

Agglutination Test

Benham and Hopkins have used this test in the identification of various strains of Candida (Monilia). Conant uses the agglutination reaction as a supplementary diagnostic test in blastomycosis.

Descriptions of other available laboratory methods of examination, such as precipitation and complement fixation tests, histologic studies, and roentgenologic examination, may be found in all standard texts on pathology, bacteriology, and medicine.

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CHAPTER III

BLASTOMYCETES: YEASTLIKE FUNGI

THE TERMS *Blastomycetes* or *yeastlike fungi* are applied to all fungi that reproduce principally by budding. We have omitted those fungi which show yeastlike growth only in tissue and when grown at 37 C., but not at room temperature. These fungi are discussed in Chapter VI. With the exception of Endomyces and Saccharomyces, they belong to the general class of Hyphomycetes or fungi imperfecti, and include the following genera:

Saccharomyces
Endomyces
Cryptococcus (Torula)
Candida (Monilia)
Pityrosporum

Castellani's simplified classification of these yeastlike fungi is based on the presence or absence of mycelium and ascospores:

1. Budding	Cryptococcus (Torula)
2. Budding and mycelium	Candida (Monilia)
3. Budding and ascospores	Saccharomyces
4. Budding, ascospores, and mycelium	Endomyces

The fungi of these genera produce budding forms not only in lesions but in culture also. Contrasted with these are the genera Blastomyces, Paracoccidiodes, and Histoplasma, which produce budding forms in lesions but moldlike growths on all media at room temperature.

This chapter is devoted to a discussion of Cryptococcus (Torula), Candida (Monilia), and Pityrosporum.

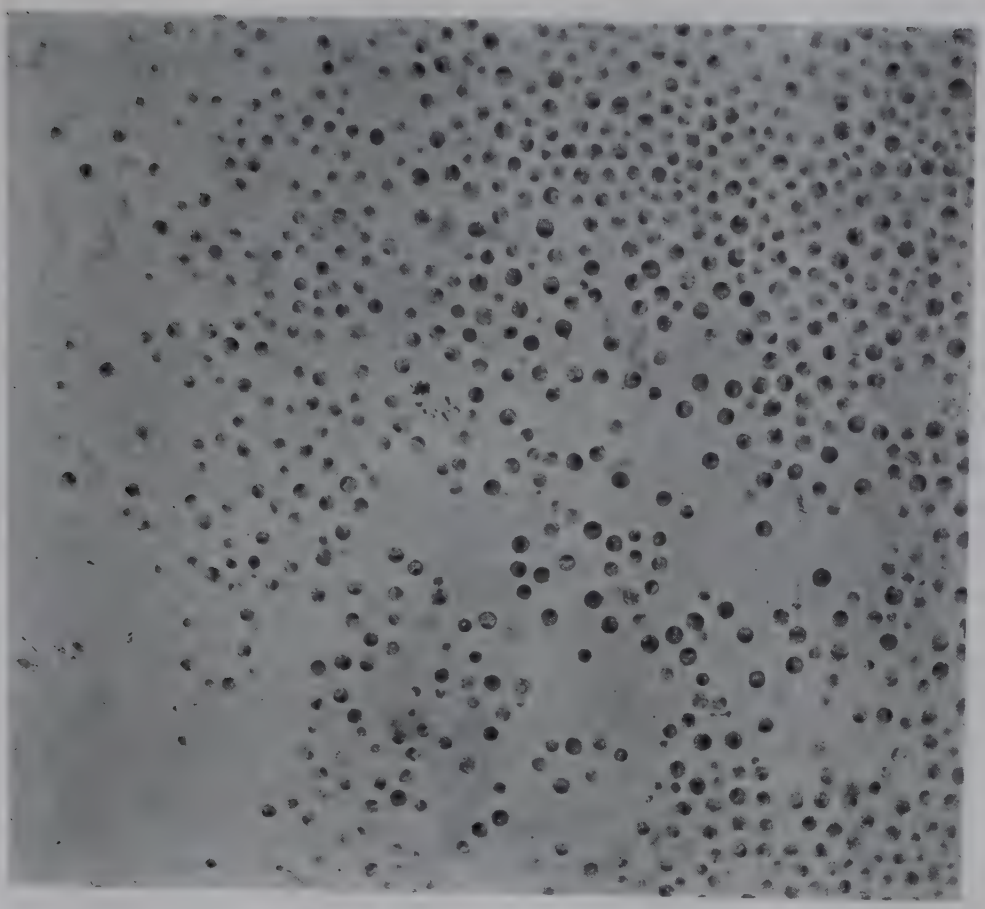

FIG. 4. BUDDING AND NONBUDDING SPORES OF CRYPTOCOCCUS NEOFORMANS. × 400

CRYPTOCOCCUS NEOFORMANS (SANFELICE; VUILLEMIN, 1901)

Synonyms: Cryptococcus hominis; Torula histolytica

MYCOLOGY

This fungus appears in tissue, spinal fluid, or pus as a single-budding ovoid to spherical organism, from 5 to 10 microns in diameter, yeastlike in character, and surrounded by a wide gelatinous capsule. The refractile capsule is a characteristic feature and is diagnostic for this fungus.

Centrifuged sediment of spinal fluid or pus should be examined while fresh by placing a drop of the material on a slide and gently pressing it to a thin film under a cover glass. The fungus is best detected under reduced light from the microscope condenser. Pus may also be placed in a drop of india ink and

quickly examinated under a cover glass while still moist. Frozen sections should be examined in wet Giemsa stain (undiluted). Recovery of Torula organisms from the blood stream has in a few cases been made by culture; they should be looked for in the urine also.

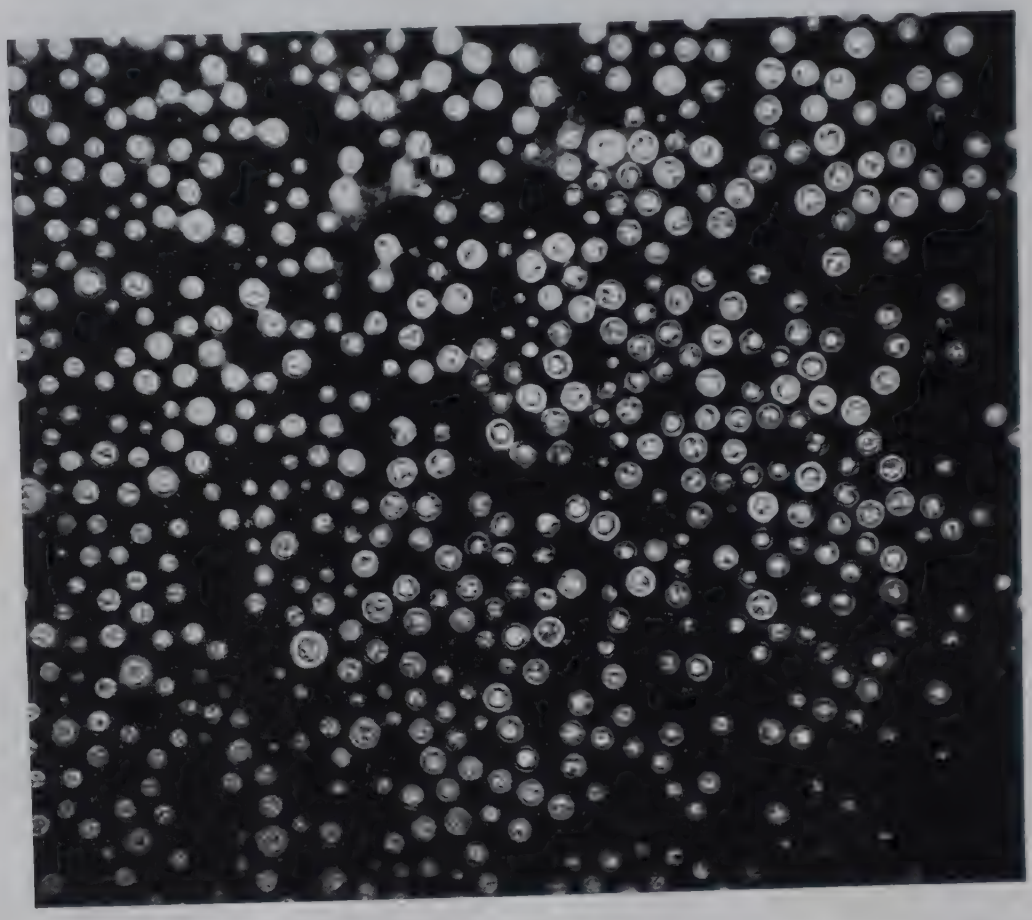

FIG. 5. CRYPTOCOCCUS NEOFORMANS. INDIA INK PREPARATION SHOWING CAPSULE. × 400

Culture material grows well on both Sabouraud's glucose agar and blood agar at room and incubator temperatures. Cultures should be kept for at least three weeks before being discarded. The culture is yeastlike, mucoid, and brownish; it contains only budding cells with characteristic capsules.

IMMUNOLOGIC REACTION

According to Benham, agglutination reactions are absent.

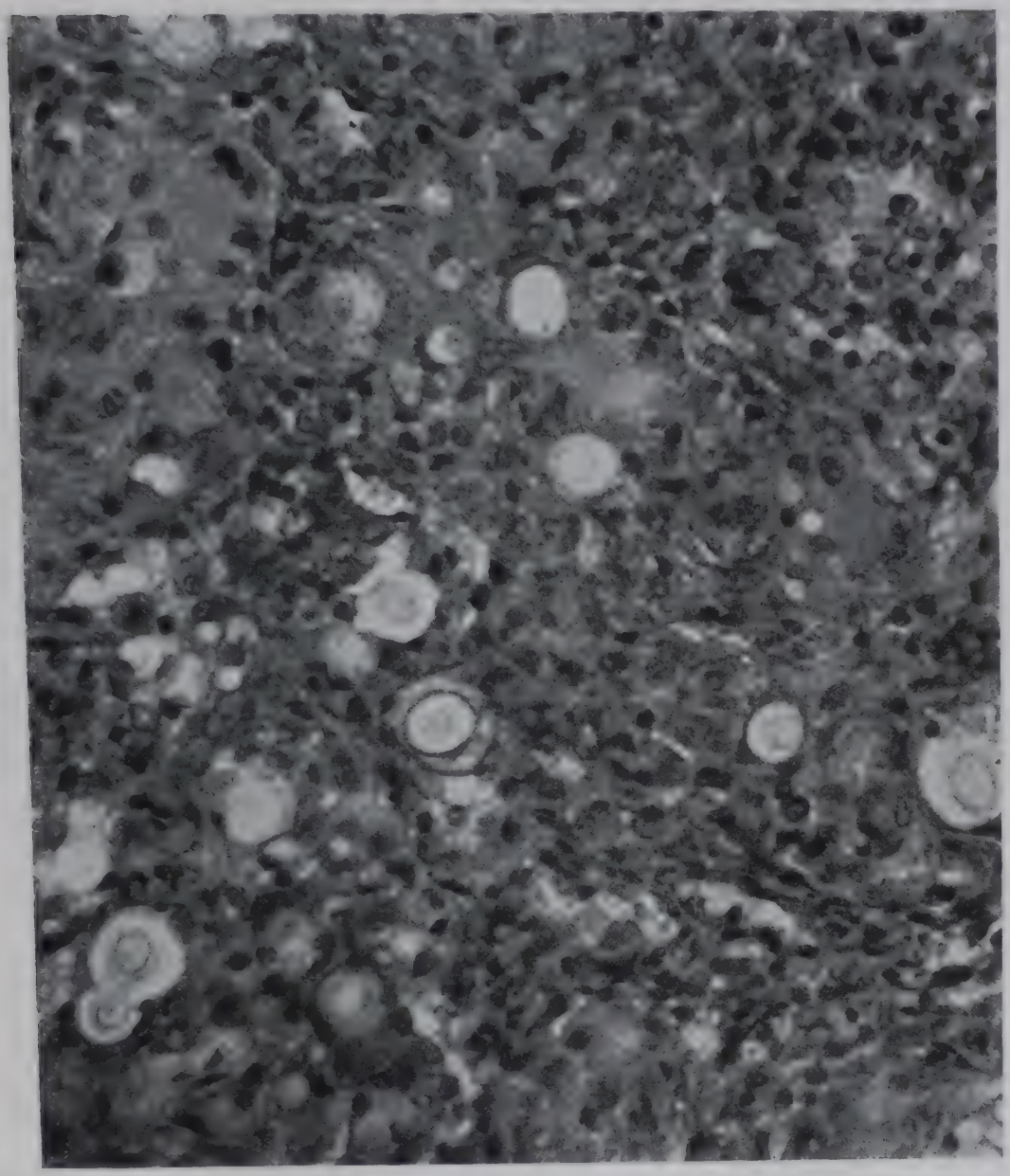

FIG. 6. CRYPTOCOCCUS NEOFORMANS IN MOUSE LUNG. × 400
Note encapsulated budding cell (Courtesy of Rhoda Benham)

Extracts of the organism are said to elicit specific cutaneous reactions in infected patients. But the diagnostic value of such tests is doubtful.

ANIMAL INOCULATION

The organism is inoculable in mice, rats, rabbits, and guinea pigs, the first two being most susceptible.

CRYPTOCOCCOSIS (TORULOSIS OR EUROPEAN BLASTOMYCOSIS)

Cryptococcosis is an infection of animal or human tissue produced by Cryptococcus neoformans. This organism reproduces only by budding, without mycelial or endospore formation. It does not ferment sugars. It seems to have a special affinity for the tissues of the cerebrospinal system but may also attack the pulmonary system, as well as other organs and tissues of the body.

Cryptococcosis in humans was first reported by Busse and Buschke from Germany (1894–95) in a patient with generalized lesions. The causative organism, Cryptococcus neoformans (Torula histolytica), was isolated from a tibial abscess. Curtis (1896) isolated this organism from a myxomatous tumor. Because the early European cases showed skin lesions, Stoddard and Cutler (1916) did not associate their cases of so-called torula meningitis with the earlier reports. Freeman (1931) and Levine (1937) reviewed several cases of central nervous system involvement. Cases of cutaneous involvement have been reported by Wile (1935), Kessel and Holtzwant (1935), and Dienst (1938). It can therefore be stated that torulosis may take the form of a generalized infection invading the central nervous system or occur as a localized infection of the skin.

Cerebrospinal Torulosis. The symptoms and signs are usually referable to the central nervous system: persistent severe headache, stiff neck, vomiting, paralysis, convulsive seizures, and decreased reflexes. Eye changes such as disturbance of vision, choked disk, diplopia, nystagmus, and strabismus are also characteristic. The spinal fluid shows both increased pressure and increased cells, chiefly lymphocytes. Elevated albumin content and globulin count and a meningitic colloidal gold curve are sometimes observed. Cutaneous lesions may accompany the meningitis; Weidman reports a granulomatous type.

Pathologically, the picture is that of a chronic leptomeningitis. The meninges are thickened, matted, and show adhe-

sions to the cerebral cortex. Exudation is scanty in amount. Tubercles are found scattered throughout the involved tissues. Little difference can be discovered microscopically between the meningeal lesions and those in the other infected organs. In the brain substance itself are found perivascular granulomatous lesions and small nodules, tubercles, or glutinous cystlike structures distributed here and there throughout the cerebral tissues. Microscopic examination reveals small spherical gelatinous spaces in which are imbedded numerous Torula organisms. Cellular reaction around these lesions is almost negligible and the glia tissue about the focus is only slightly increased. Large mononuclear and lymphocytic cells are found in and about the lesions. Outside the brain, the lesions of pulmonary and other forms of torulosis consist of small tubercles or nodules surrounded by what appear to be clear zones or halos. The organism may be observed both intracellularly and extracellularly.

The disease is slowly progressive and fatal, death usually occurring as a result of respiratory failure.

Pulmonary Torulosis. This may be primary or secondary. Sheppe records the only known case of the former type. The secondary form of the disease occurs in approximately 42 per cent of recorded cases. The clinical picture may be confused with that of tuberculosis, syphilis, or other pulmonary mycoses. There is nothing characteristic about the pulmonary symptoms, signs, or x-ray picture of patients with cryptococcosis. The diagnosis of primary pulmonary cryptococcosis is usually made by cultural studies of the sputum and secretion obtained by bronchoscopic examination. This should be done in every case of obscure pulmonary infection. The diagnosis of secondary pulmonary cryptococcosis is not so difficult to make.

Other Forms of Torulosis. The organism may secondarily involve the spleen, liver, kidneys, and mesenteric glands. In fact, an enlarged spleen and unexplained typhoid-like fever should put the examiner on the alert for the presence of a

systemic yeastlike infection in cases where the possibility of typhoid, undulant fever, or similar infectious diseases has already been eliminated. Superficial *café au lait* patches covered with furfuraceous scales may be seen on the eyelids, the neck, the flexures of the elbows, and the thighs. Other skin manifestations are deep granulomatous lesions simulating

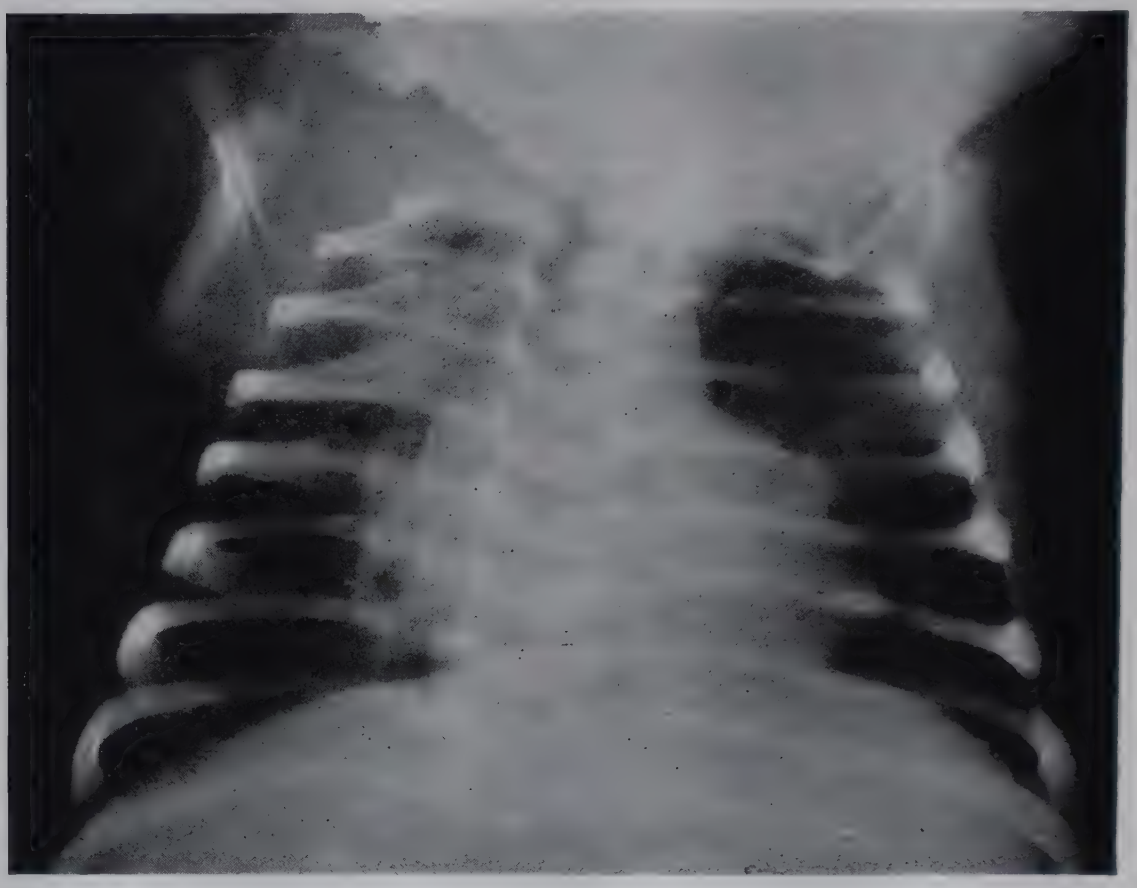

FIG. 7. PULMONARY CRYPTOCOCCUS
Showing interstitial pneumonitis, focal atelectasis and a large granulomatous lesion in the right upper lobe (Courtesy of E. B. D. Neuhauser and Arthur Tucker. Am. J. Roentgenol. Vol. LIX, No. 6, June 1948)

those of syphilis, tuberculosis, and coccidioidomycosis. Differential diagnosis can be made only on the basis of mycologic studies. The blood findings are not distinctive. A moderate leukocytosis (count of 8,000 to 25,000) is present; the number of polymorphonuclear cells may or may not show slight increase.

Treatment. The *cutaneous* and *subcutaneous* lesions if local-

ized are best treated by excision and drainage followed by filtered semi-intensive roentgen ray therapy. This may be supplemented by iodide therapy to a point of intolerance, or by sulfonamide or penicillin or both, to combat secondary bacterial infection. The sulfonamides may also be effective in cryptococcosis in intensive doses. Improvement with clinical trial of the sulfonamides have been reported by Conant et al., Marshall and Teed, and others. Keeney has shown that complete inhibition of the growth of C. neoformans in vitro can be obtained with very high concentrations. Treatment with sulfonamides should be continued for several weeks after all signs of clinical activity are gone. *Cryptococcosis of the central nervous system* has a very poor prognosis. No specific treatment is known. Iodides in any form, trivalent and pentavalent arsenicals, antimony compounds, thymol and gentian violet have proved ineffective. Vaccinotherapy to stimulate immunity, since patients with cryptococcosis have proved to have difficulty in producing immune bodies, may be given a trial. Supportive therapy should be stressed. Repeated lumbar punctures may relieve symptoms. Sulfonamides, preferably sulfadiazine, in doses sufficient to maintain a blood level of 8 to 12 mg. per 100 cc. of blood should be administered throughout the course of the disease and for at least two weeks after all symptoms have disappeared. If the sulfonamides do not prove effective enough penicillin intramuscularly and intrathecally may be supplemented. The reports as to the effectiveness of penicillin in cryptococcosis are controversial. Keeney states that this drug does not inhibit the growth of C. neoformans in vitro. Meyer has reported that cultures of the organism are killed in vitro by penicillin. Hobby and his associates have also found that C. neoformans is sensitive to penicillin in vitro.

Candida Albicans (Robin; Berkhout, 1923)

Synonyms: Monilia albicans; Candida; Monilia

Candida was first described as a human pathogen by Langen-

beck in 1839. In the course of postmortem examination of a typhoid patient, he found the parasite in patches of thrush on the oral mucous membrane, the pharynx, and throughout the intestinal tract. Charles Robin in 1843 gave to the organism the name of Oidium albicans. In 1905 Castellani revealed this parasite to be a cause of bronchomoniliasis. Since then,

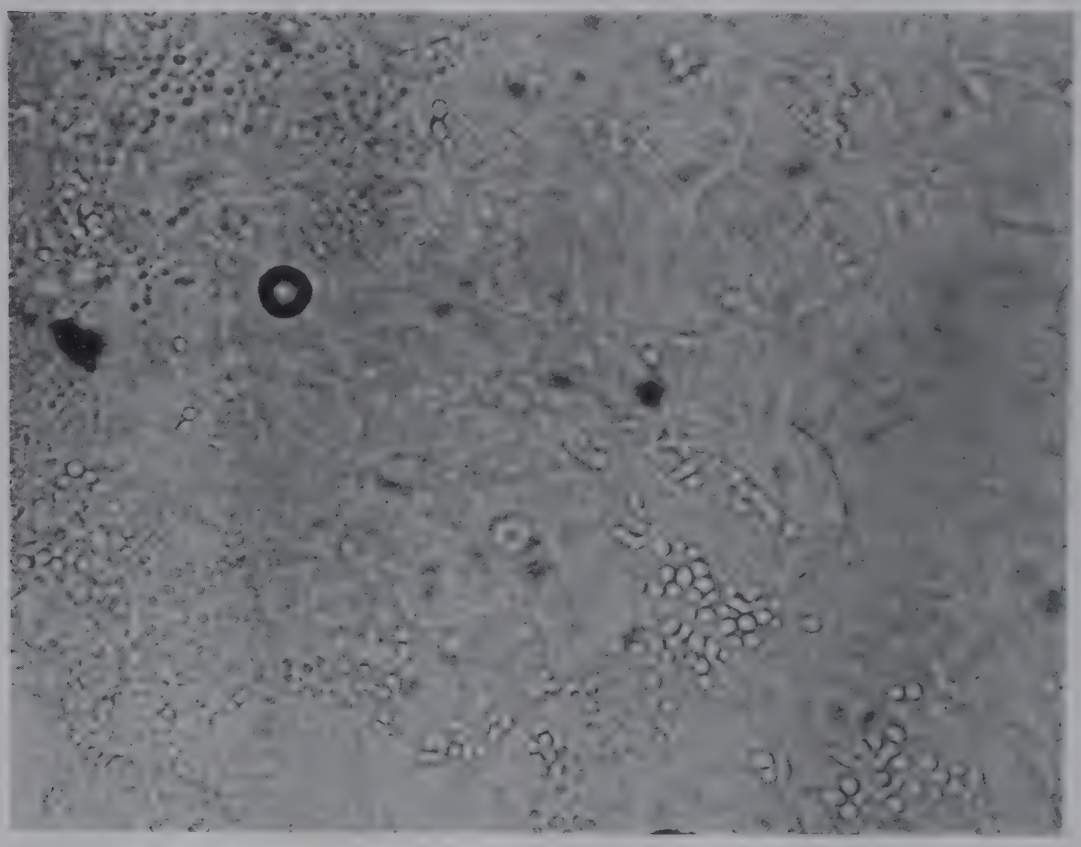

FIG. 8. CANDIDA IN SCRAPINGS FROM CHRONIC PARONYCHIA AND MONILIASIS OF THE SKIN

certain diseases of the skin and other tissues have been traced to Candida albicans and other members of the species.

MYCOLOGY

Candida appears in the sputum, the skin, the nails, and the buccal and the vaginal mucosa as small round and oval budding yeastlike cells. The sputum is examined in fresh preparation on a cover glass or smeared on a slide and given a Gram stain.

Mucous patches should be placed in a drop of water or 10 per cent potassium hydroxide and examined under a cover glass. Skin and nail scrapings should be examined in 10 per cent potassium hydroxide, heated slightly, if necessary, to clear the specimen. On direct microscopic examination, the skin, feces, or sputum, treated with potassium hydroxide, shows numerous budding and nonbudding spores. Hyphae may be present, particularly in preparations from skin or nails. Mycelial ele-

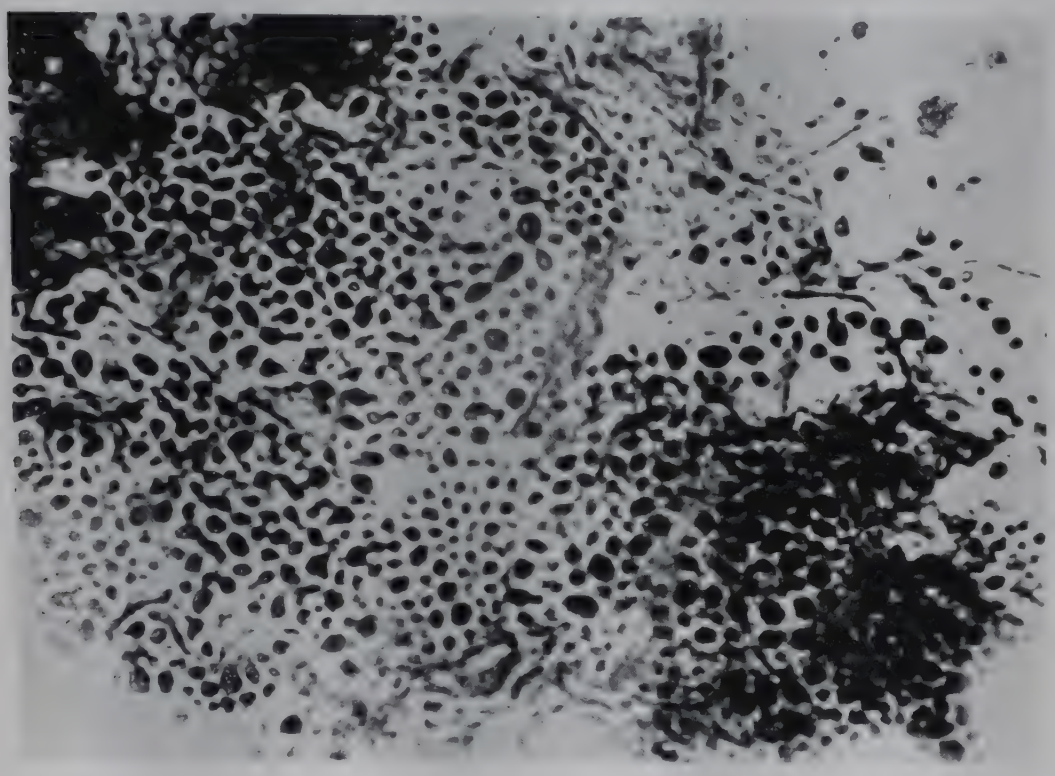

FIG. 9. CANDIDA IN SCRAPINGS FROM HAIRY TONGUE (STAINED PREPARATION)

ments are seen occasionally, with budding cells at the points of constriction. The mycelial threads may be short and abortive, or long and interwoven.

On Sabouraud's glucose agar, growth takes place at both room and incubator temperatures. When a pure culture is obtained, it may be transferred to corn meal agar in a Petri dish by cutting the surface of the agar with a small amount of

FIG. 10. BUDDING AND NONBUDDING SPORES IN EARLY GROWTH OF CANDIDA ALBICANS. × 600

the culture on a straight wire. Examination of the streak through the bottom of the Petri dish with the low-power microscope will show chlamydospore-bearing mycelium. Microscopically, clusters of spores are disclosed massed along the hyphae. Chlamydospores are present. No ascospores are seen. Hyphae and chlamydospores are better developed on corn meal agar than on dextrose. On corn meal agar, a deep stab with a needle containing the cultural growth will produce a growth simulating an inverted pine tree. This is characteristic for this organism.

On Sabouraud's glucose broth no surface growth develops. On streaked blood agar plates the colony is dull gray and of medium size. Acid and gas are produced in glucose and maltose; in sucrose, acid alone.

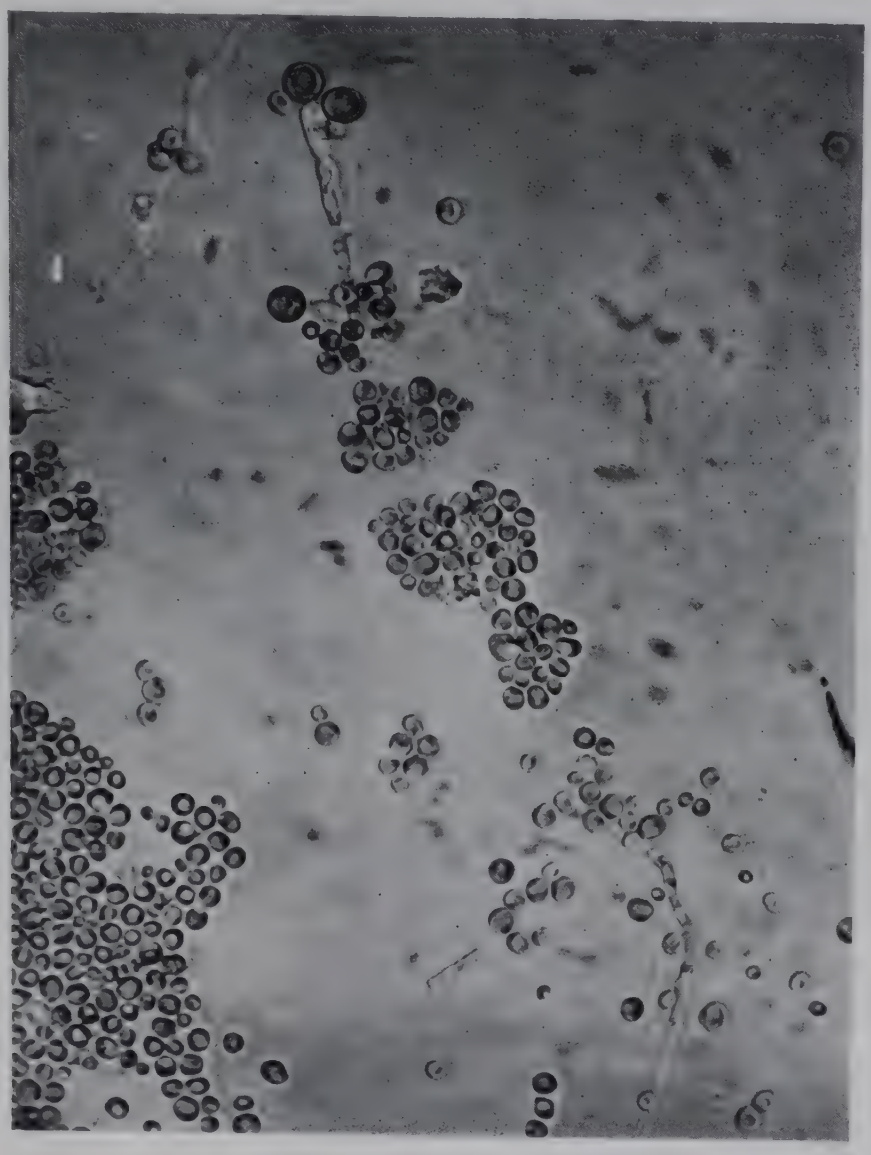

FIG. 11. CLUSTERS OF SPORES AND CHLAMYDOSPORES ABOUT MYCELIUM IN CANDIDA ALBICANS. × 400

ANIMAL INOCULATION

Intravenous injection of 1 cc. of a 1 per cent suspension of the organism will kill a rabbit within four to five days.

In some strains, positive agglutination reactions have been obtained by Benham.

Only six species can be identified in freshly isolated cultures:

Candida albicans
Candida tropicalis
Candida parakrusei
Candida krusei
Candida stellatoides
Candida pseudotropicalis

IMMUNOLOGIC REACTION

The cutaneous reaction is of limited diagnostic value. A positive reaction is obtained in 46 to 54 per cent of patients without obvious infection, in 57 per cent of patients with localized cutaneous moniliasis, and in 52 per cent of patients with gastro-intestinal moniliasis. The percentage of positive reactions to the test increases in progressively older age groups. Lewis and Hopper have found that 75 per cent of apparently normal persons between 51 and 60 years of age show a positive cutaneous reaction.

MONILIASIS

The name moniliasis is given to a group of disorders caused by organisms belonging to the genus Candida (Monilia). Dissemination by way of the blood stream occasionally gives rise to a systemic moniliasis, but the cutaneous, the mucous membrane, and the visceral forms of the disease are more common.

Cutaneous and Mucous Membrane Moniliasis. Many forms of skin eruption formerly diagnosed as eczema, intertrigo, toxic dermatitis, and under the names of certain other skin disorders, are now known to be moniliasis. Both a generalized and a localized form of the disease occur.

Localized cutaneous moniliasis takes many forms, appearing variously as chronic paronychia, erosio interdigitalis, perlèche,

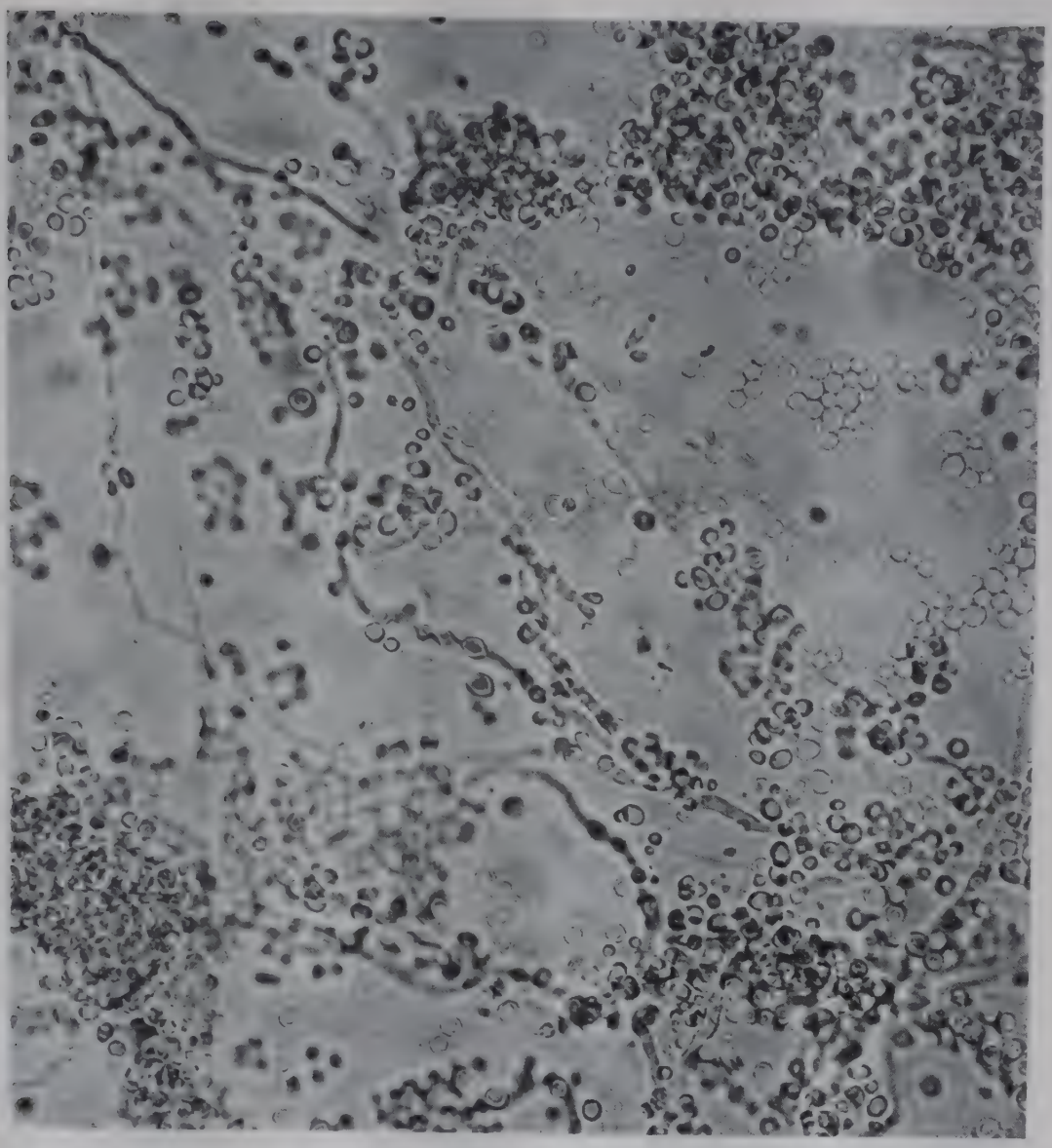

FIG. 12. CLUSTERS OF SPORES ABOUT MYCELIUM IN CANDIDA ALBICANS. × 400

intra-oral thrush, superficial glossitis, water bath dermatitis, eczema, vaginitis, or pruritus ani.

Chronic paronychia is a common, resistant condition that involves the fingers chiefly. The nails show transverse ridges with eventual brownish discoloration, thickening, and distortion. The proximal portion of the nail edge may show softening, and the soft tissue about the bases and nail edges is inflamed and thickened. Tenderness on pressure is another sign. Chronic paronychia alone may be present or occur together

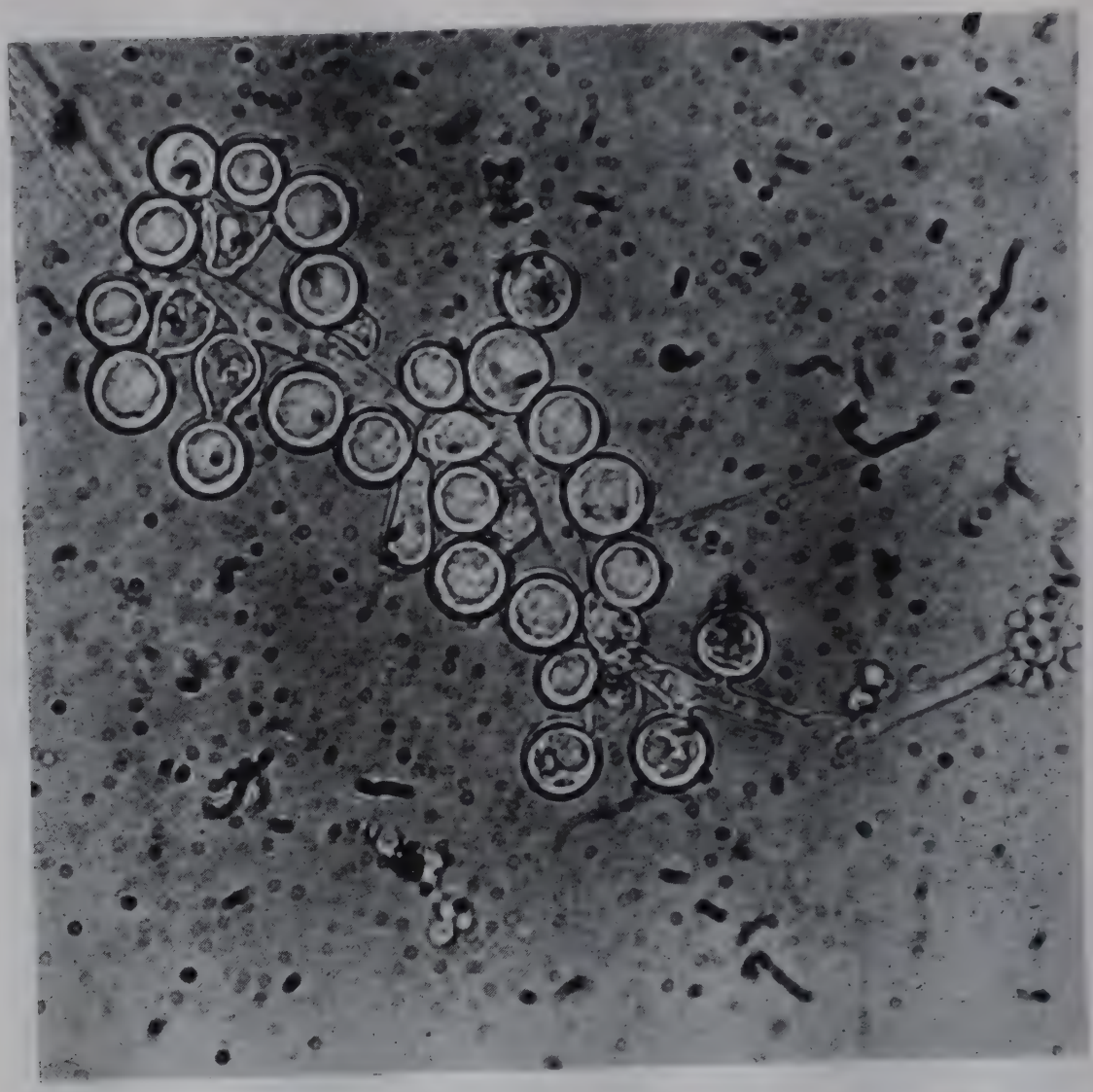

FIG. 13. CHLAMYDOSPORES IN CANDIDA ALBICANS (OLD BROTH CULTURE). × 500

with erosio interdigitalis. It is differentiated from onychomycosis by the absence of crumbling and yellowish discoloration, the presence of soft-tissue thickening and inflammation, and the retention of nail luster. Chronic paronychia affects chiefly domestics, housewives, bartenders, and dishwashers.

Erosio interdigitalis blastomycetica is an intertrigo affecting the web between the third and fourth fingers of the hand, usually the right hand. The lesion has a bright red base with a moist macerated surface and a desquamating border. Housewives, dishwashers, and domestics are chiefly affected.

Perlèche, another form of intertrigo, is seen in the angles of the mouth. The base of the lesion is bright red, the surface sometimes showing a pellicle of skin. Fissures are common. Some cases of perlèche are said to be due to streptococcus, others to avitaminosis B.

Intra-oral thrush, occurring anywhere in the mouth, is rela-

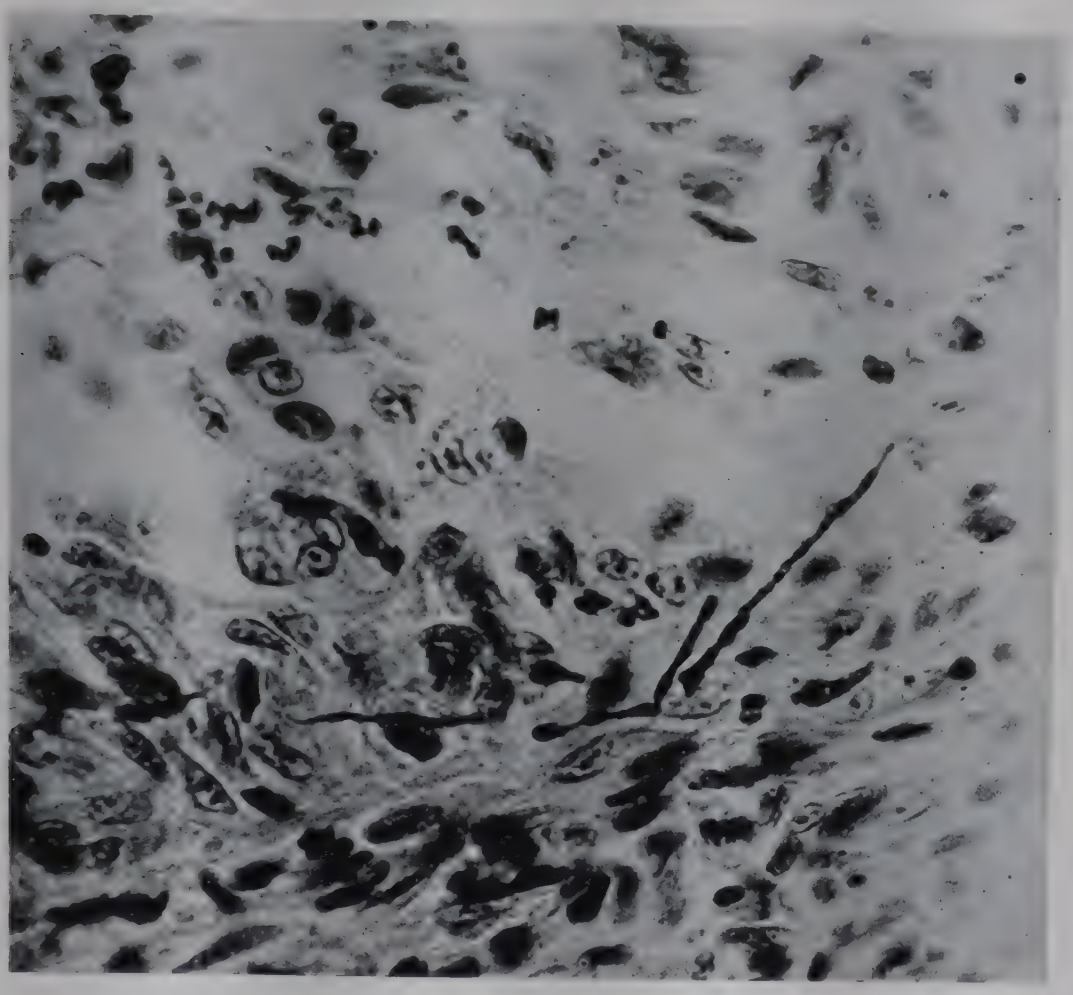

FIG. 14. CANDIDA IN TISSUE. × 900

tively more common in infants and children. It is seen as a loosely adherent whitish membrane. When removed, treated with potassium hydroxide, and examined microscopically, it is seen to harbor a yeastlike organism.

Water bath dermatitis may develop following prolonged im-

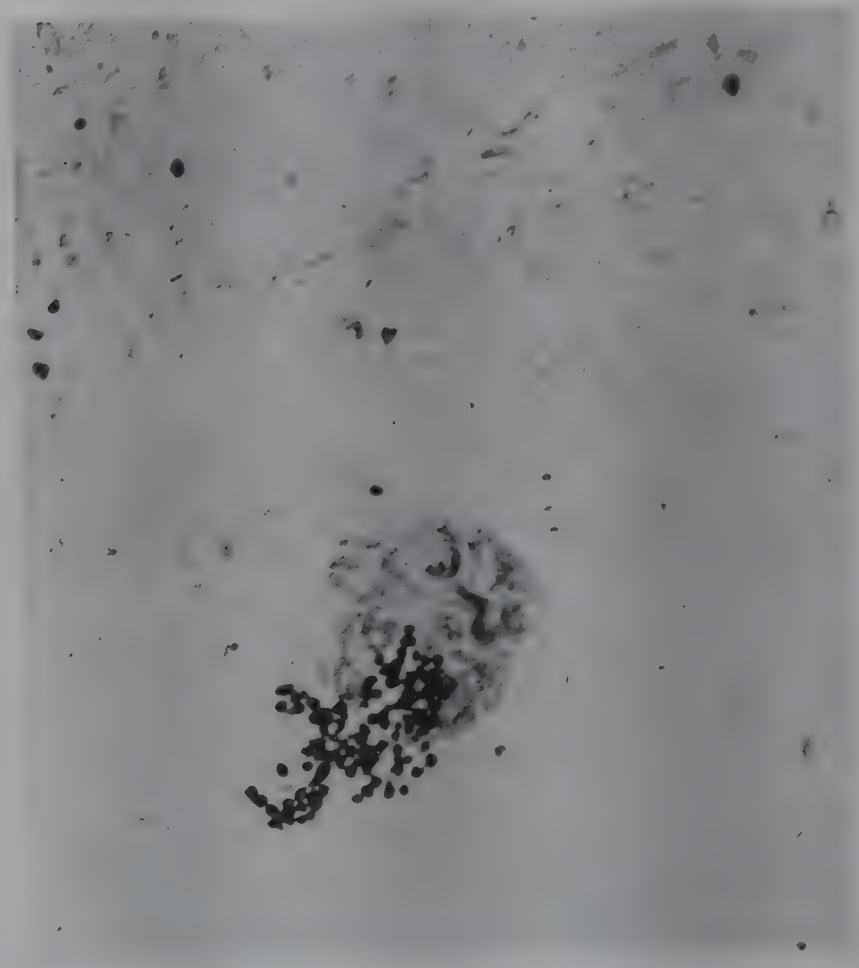

FIG. 15. CANDIDA ALBICANS IN LUNG ABSCESS OF RABBIT

Produced by intravenous and intrapulmonary injection with micro-organism from human bronchopulmonary moniliasis

mersion in water or continued use of wet applications of a bland nature. The macerated skin, when peeled off, shows a red base. Kumer and others have reported finding Monilia albicans and other yeastlike organisms in the lesions; whether these were pathogens or were living a saprophytic existence was not ascertained.

Vaginitis, with itching and low-grade inflammation accompanied by a thin discharge, may be caused by Candida albicans. A whitish exudate may be superimposed on a red inflammatory base. Vaginitis alone may be present or occur in combination with pruritus ani. In infants it may be found with thrush.

The Monilia organism, however, may inhabit the vaginal region as a saprophyte.

Generalized cutaneous moniliasis is less common than the localized form. Occurring more frequently in children than in adults, the clinical picture is characterized by perlèche and glossitis, a widespread cutaneous eruption accompanied by inflammation and pustules and also by thinning of the hair, par-

FIG. 16. CHRONIC PARONYCHIA CAUSED BY CANDIDA ALBICANS

ticularly of the scalp. The course of the disease is usually little affected by treatment and is frequently fatal.

Moniliids are vesicular, erythematous, or exudative sterile lesions that may appear on the hands as a result of dissemination of Candida albicans through the blood stream. The focus may be found elsewhere on the skin or, according to Hopkins, in the gastro-intestinal tract.

Bronchopulmonary Moniliasis. Castellani (1905) first re-

FIG. 17. CHRONIC PARONYCHIA CAUSED BY CANDIDA ALBICANS

ported bronchopulmonary moniliasis in Ceylon. Numerous cases have since been reported from various parts of the world, especially the tropics. In this country, the first case was reported from Baltimore in 1915 by Boggs and Purcoff. Castellani describes the disease as occurring in a mild, intermediary, or severe form; the clinical picture in each is different.

The mild and intermediary types are characterized by dyspnea and cough of varying severity. Hemoptysis may occur. The mild type is not usually febrile, but in the intermediary

form a slight irregular rise in temperature may be noted. Bodily nutrition is not markedly affected. The chest signs are those of a chronic bronchitis. Recovery may be spontaneous, the process may remain stationary, or the disease may progress to the severe form, which takes a chronic course that usually ends in death. Cough, expectoration, and hemoptysis, with hectic fever, night sweats, and emaciation, characterize the terminal phase. One or both lungs and frequently also the pleura may

FIG. 18. EROSIO INTERDIGITALES BLASTOMYCETICA

be involved, with evidence of consolidation and pleural thickening. Roentgenologic findings resemble those seen in other pulmonary infections, but the more frequent involvement of the lung bases serves to differentiate the disease from tuberculosis. Diagnosis can be made on the basis of direct microscopic examination of sputum, and preferably bronchial secretion, cultural studies, animal inoculation, and biochemical reactions.

FIG. 19. MONILIASIS OF FOOT

Treatment. The treatment of moniliasis is, at best, not too successful. The known antibiotics and newer chemotherapeutic agents have not proved effective. It is our belief that successful treatment will depend upon the discovery of agents which through either stimulation of immune reaction or direct fungistatic or fungicidal action will bring about a cure of the disease that at present is most resistant, particularly in the generalized cutaneous and systemic forms.

FIG. 20. MONILIASIS OF GROIN

1. Gentian violet (1 per cent aqueous solution), for thrush and vesicular or pustular skin lesions. Lewis reports successful use of suppositories containing 2 grains of gentian violet in cases of monilial vaginitis.

2. Potassium permanganate mouth wash (1:10,000), for thrush. Good results have been obtained by the author with 0.5 to 1 per cent solutions for moist cutaneous lesions.

3. Sodium perborate soaks (3 drachms to ½ glass of water), for the hands and as a mouth wash in thrush. Sodium perborate paste has been successfully used in chronic paronychia and in erosio interdigitalis (Greenwood and Rockwood).

FIG. 21. MONILIASIS IN SUBMAMMARY AREAS

4. Mercurochrome solution (5 per cent), or the formula below. This has been used successfully by the author in chronic paronychia, erosio interdigitalis, and the other localized forms of cutaneous moniliasis:

		Gm. or cc.
℞	Mercurochrome crystals	0.6
	Aqua	1.2
	Acidi salicylici	2.0
	Petrolati	
	Lanolini *aa ad*	30.0
ℿ		

5. Fatty acids. The sodium salts of propionic, valeric, caprylic, capric, and undecylenic acids are fungistatic and fungicidal in varying degrees for the different pathogenic fungi

when tested in vitro. Of these fatty acid salts, sodium caprylate is particularly effective against Candida (Monilia) albicans. Keeney therefore recommends a 20 per cent aqueous solution of sodium caprylate adjusted to a reaction of *p*H 7.4, for the lesions in intra-oral thrush. Our experience with 2 cases of intra-oral thrush associated with cutaneous and onychial involvement did not parallel the results reported by Keeney. However, more cases need to be treated before a correct evaluation of the effectiveness of such treatment can be made.

Alter et al. recommend the following jelly in monilial vulvovaginitis.

	Gm. or cc.
Calcium propionate	9.5
Sodium propionate	9.5
Propionic acid	1.0
Glycerin	10.0
Bentonite	32.0
Water	38.0

6. Iodides (orally, intravenously, or by inhalation). These are not usually necessary except in extensive cutaneous involvement or in the case of accompanying moniliids. Ethyl iodide inhalation is the most effective measure in broncho-pulmonary moniliasis, systemic moniliasis, and generalized moniliasis (see p. 53).

7. Roentgenologic therapy, in paronychia, onychia, and sometimes perléche. An average weekly dose of 50 to 75 r unfiltered is used. In our opinion this treatment is effective not because of its fungistatic and fungicidal action but because of its effect on chronic inflammatory tissue.

8. Vaccine therapy. This has not proved successful. Successful quantitative intracutaneous therapeutic desensitization with trichophyton and monilia extracts, alone and in combination, have been reported by Sulzberger, Wise, Kerr, Paicher, and others. Olah's attempts at autovaccine therapy in

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FIG. 22. MONILIASIS OF KNEE

onychia and paronychia were unsuccessful. Oidiomycin inoculations, in dilutions ranging from 1:1,000, 1:500, 1:100 to 1:50, were used by Lewis and his co-workers in a series of 48 patients, with no improvement in the majority of cases.

The patient with cutaneous moniliasis must also be warned against dishwashing, handling of vegetables, and similar tasks without the protection of rubber or cotton gloves. Intake of starchy foods should also be reduced.

GENERALIZED CUTANEOUS AND SYSTEMIC TYPES

Therapy should be directed toward the eradication of all foci of infection when possible. Complete study of the patient

with particular reference to diabetes, nutritional disorders, poor hygiene, and parathyroid disease should be made. X-ray examination of the chest for bronchopulmonary involvement should be included.

A high vitamin, high calorie diet, reinforced by components of vitamin B complex and liver therapy, is helpful.

Iodide therapy, particularly ethyl iodide inhalation, has proved most effective in bronchopulmonary moniliasis, probably because the coefficient of distribution between the alveolar air and the blood in the lungs is sufficiently high to allow introduction of a relatively large amount of iodine into the blood

FIG. 23. MONILIASIS OF MOUTH AND SKIN IN A FATAL CASE OF SYSTEMIC MONILIASIS

stream. It has also been demonstrated that a small proportion is returned in the venous blood so that the tissues are exposed to relatively large amounts of iodine. In bronchopulmonary moniliasis, inhalation therapy is a more direct route. The initial dose of ethyl iodide is 1.5 cc. (3 Gm.). This is increased by 0.5 cc. (1 Gm.) per dose until 4 cc. (8 Gm.) is reached.

This may be given in one or in divided doses. Treatment is given on two successive days and skipped on the third day to avoid cumulative effect. A mineral oil spray to avoid irritation of the throat may be used once or twice a day. The inhaler of choice* is designed to allow a comfortable mixture of ethyl iodide and air to be inhaled. It is important that the ethyl iodide be free from impurities, particularly phosphorus.† This can be accomplished by proper distillation. *Ethyl iodide*

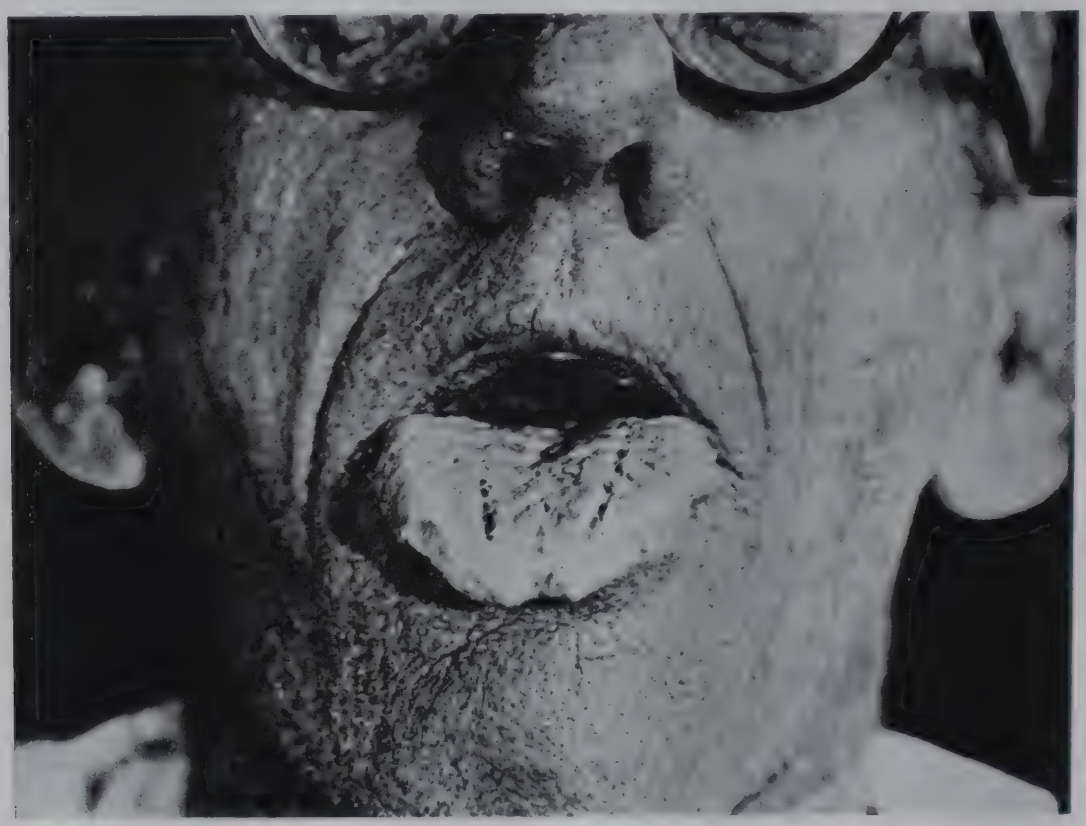

FIG. 24. MONILIASIS OF MUCOUS MEMBRANE OF MOUTH IN FATAL CASE

should never be administered to patients suffering from pulmonary tuberculosis, toxic goiter or nephritis. The number of treatments varies with the site of the infection, its duration, and the nature of the invading organism. Infections caused by the yeastlike fungi are relatively more resistant to treatment.

* The inhaler may be obtained from Warren Collins, Boston, Massachusetts.

† Purified ethyl iodide may be obtained from Burnham Soluble Iodine Company, Auburndale, Massachusetts.

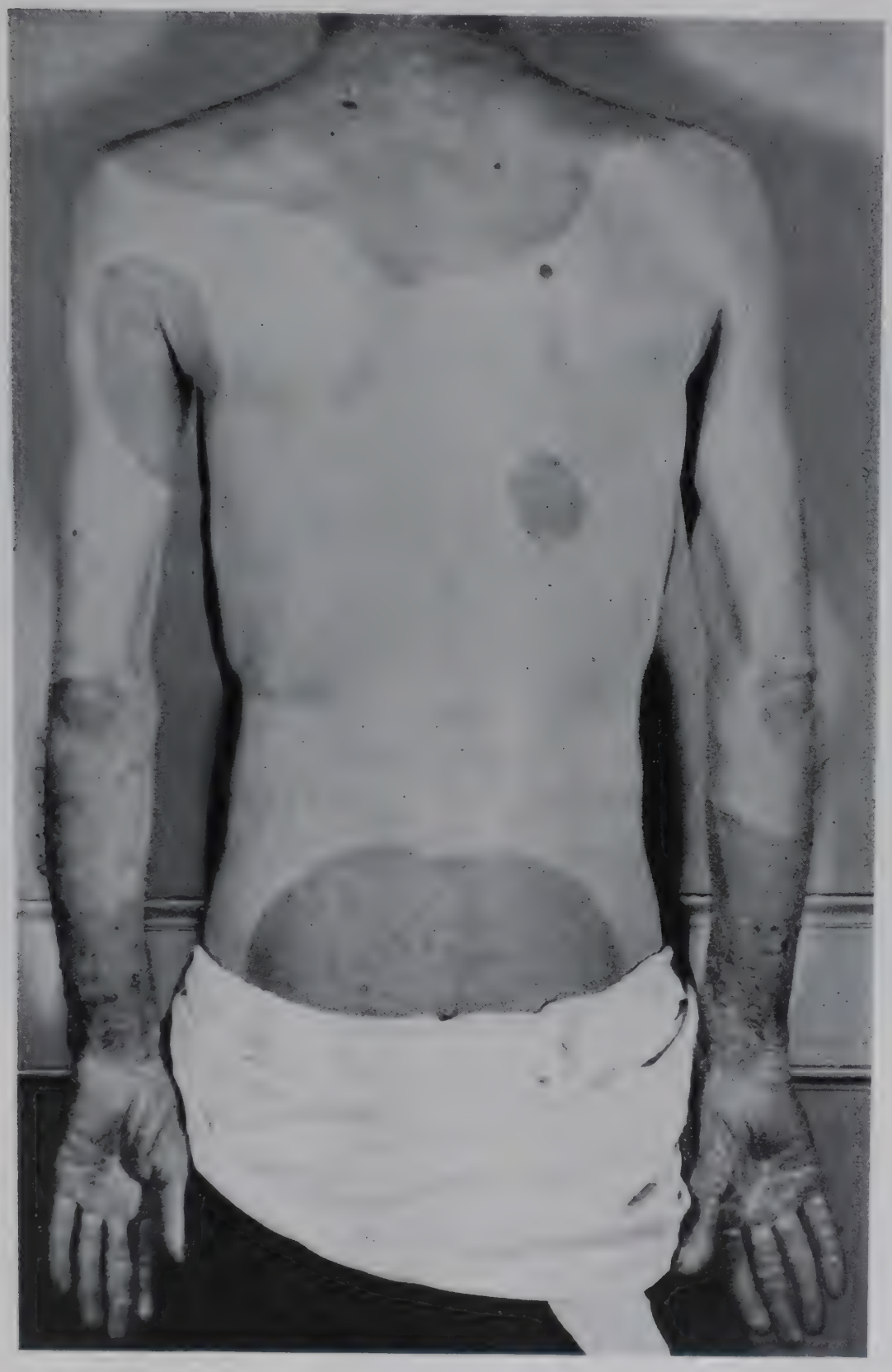

FIG. 25. GENERALIZED MONILIASIS (Fatal Case)

The most common complication is the acneform eruption, on the face and upper trunk. The eruption usually disappears a few days after the drug has been discontinued. Treatment may be resumed without ill effect in most cases. A vesicular, bullous eruption should be a signal to discontinue the drug. Peripheral neuritis is a rare complication and is probably due

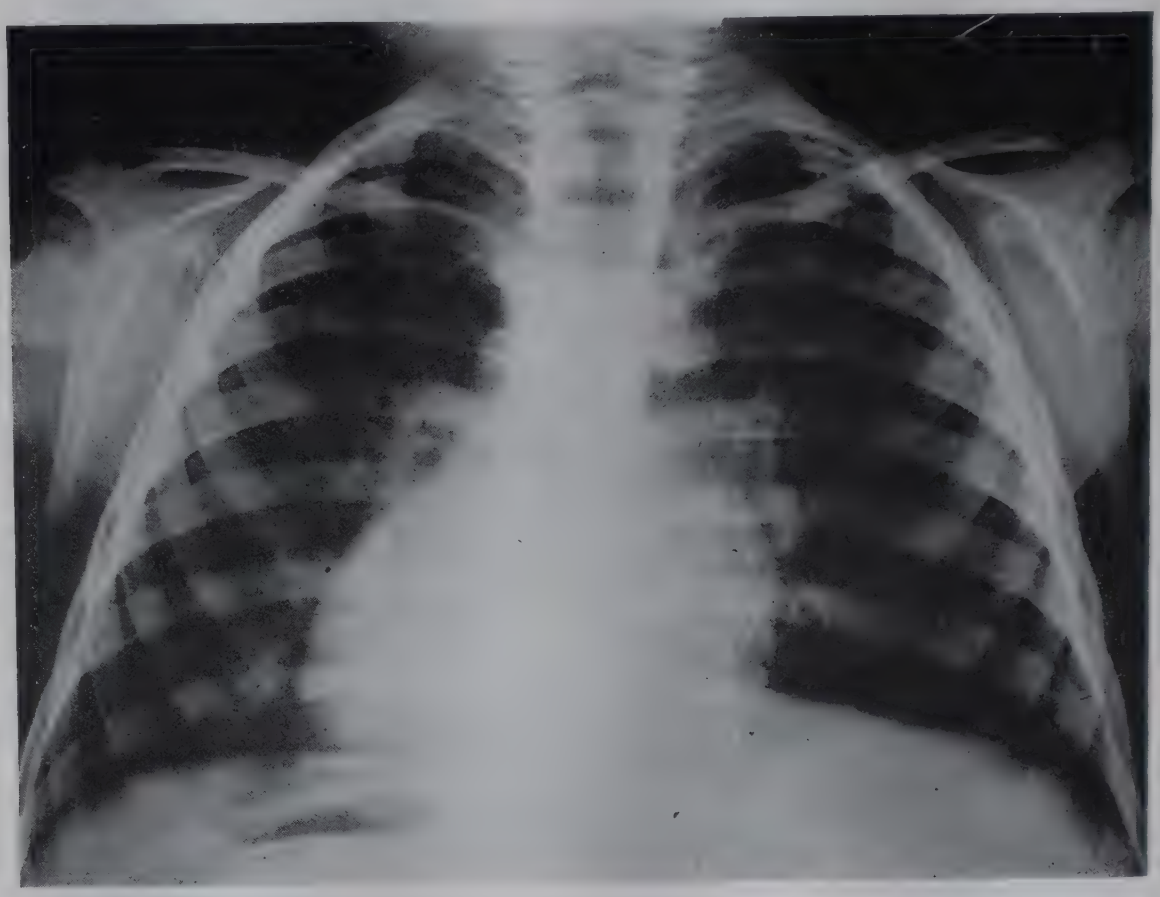

FIG. 26. BRONCHOPULMONARY MONILIASIS
(Courtesy of E. B. D. Neuhauser and A. Tucker)

to the ethyl radical. Treatment with ethyl iodide should be discontinued when peripheral neuritis occurs.

Other forms of iodine therapy may be used. Saturated solution of potassium iodide starting with 15 drops three times a day orally and increased 3 drops daily to the point of tolerance is most commonly administered. Sodium iodide intra-

venously in 1 Gm. daily doses may be used. Tincture of iodine in milk or water may be given orally, starting with 5 drops three times a day and increasing the dose to the point of tolerance.

Martin and Smith recommend desensitization with monilial vaccine in hypersensitive patients before any course of iodine therapy is started (see discussion on treatment of blastomycosis, p. 152).

Hiat and Martin describe a dramatic recovery in a case of bronchopulmonary moniliasis treated with anti-*Candida albicans* rabbit serum. The patient was given injections subcutaneously, beginning with 0.1 cc. of a 1:10 dilution, and the dose increased by 0.1 cc. daily until 0.9 cc. was reached. This favorable response was obtained in a patient with negative skin test to Candida albicans vaccine, a negative complement-fixation test and a positive immediate reaction to an anti-*Candida albicans* rabbit serum. Our experience with this form of treatment is limited to two cases of generalized cutaneous moniliasis. We did not obtain the good results reported by Hiat and Martin. More cases need to be treated before proper evaluation can be made.

One of the authors (J. H. S.) is using blood serum from patients recovered from localized moniliasis such as chronic paronychia in the treatment of systemic moniliasis. The results will be reported later.

Pityrosporum Ovale

This is a yeastlike organism originally described by Malassez in 1874. It is also known as the bottle bacillus. MacLeod and Dowling in 1928 succeeded in cultivating it but could not keep transplants alive. Previously, Unna, Engman, Castellani, Templeton, and others had had similar experience. Moore recently reported success in approximately 10 per cent of cases by culturing the organism on wort agar (Difco), and also succeeded in inoculating it on other media from a good

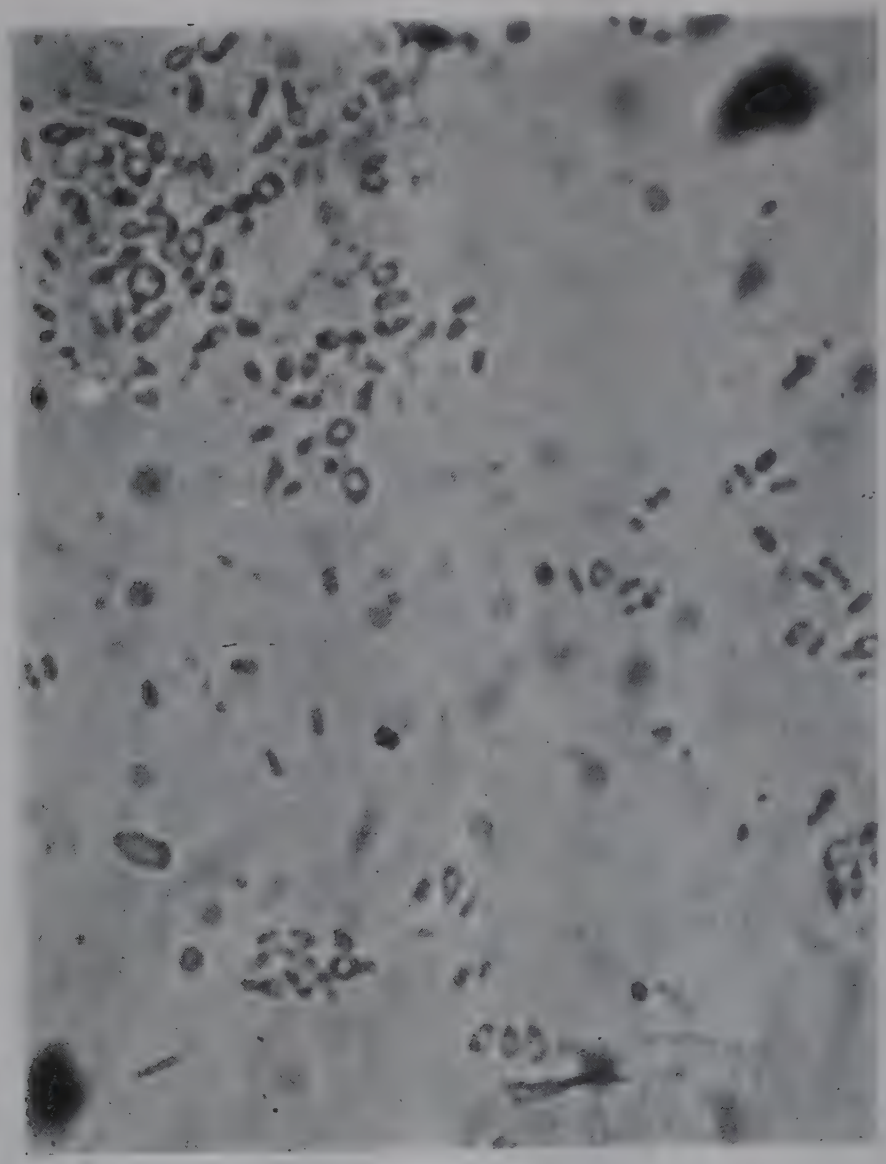

FIG. 27. PITYROSPORUM OVALE IN SCALE. STAINED WITH METHYLENE BLUE. × 1100
(Courtesy of Rhoda Benham)

primary growth on the wort. The following medium is recommended by Lewis and Hopper for subculture when it is desired to keep the growth alive:

	Gm. or cc.
Technical maltose	20.0
Technical dextrose	20.0
Peptone	10.0
Agar-agar	18.0
Distilled water	1,000.0

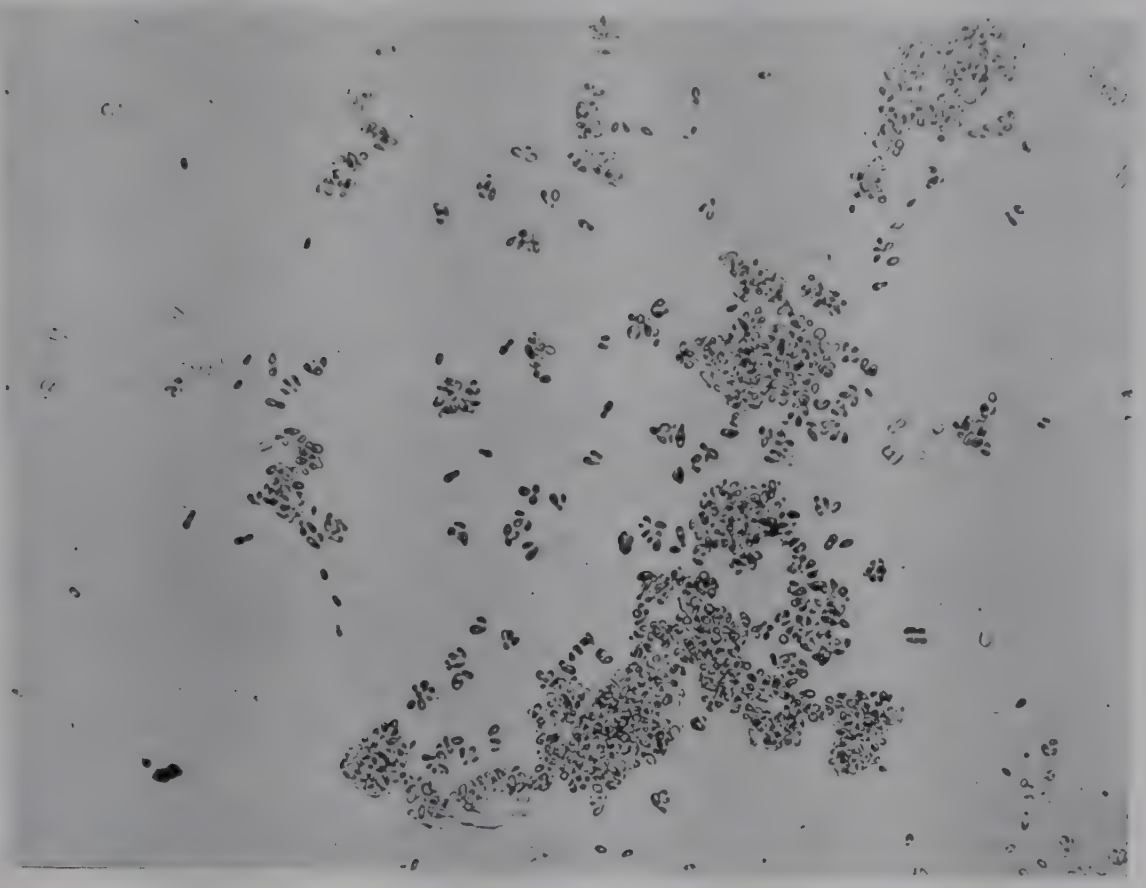

FIG. 28. PITYROSPORUM OVALE
Culture on wort agar and ether extract of oleic acid. × 700. (Courtesy of Rhoda Benham)

Benham recommends the addition of butter since she has shown that Pityrosporum ovale requires a fatty environment.

The colonies vary in color from a light ochraceous salmon to pinkish buff. At the end of forty days, the culture measures 2 cm. The individual cells as seen on culture mounts are bottle-shaped and vary in size from 3 to 15 microns in diameter. According to Moore, Keil, Engman, and Engman, inoculation of animal and human subjects with the organism from their culture, which they called P. ovale, produces a clinical and pathologic picture simulating seborrheic dermatitis. Their findings still await confirmation. In a survey of scalps of 100 patients, MacKee, Lewis, Spence, and Hopper found Pityrosporum ovale on 70 per cent normal scalps and on 66 per cent

of scalps on which there was a concomitant skin disease. In the majority of examinations, it was found that there was a greater number of colonies grown from scalps with dandruff than from normal scalps. They also found that Pityrosporum ovale is also a common inhabitant of the skin.

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CHAPTER IV

GENUS MICROSPORUM (GRUBY, 1843)

Of the numerous species of Microsporum, only three will concern us here:

Microsporum audouini (human type)
Microsporum canis (lanosum) } (animal type)
Microsporum gypseum (fulvum) }

The other species of this genus, in the authors' opinion, hardly merit discussion, since they are either rare or in all probability identical with these three.

Mycology

Generally parasitic in the hairs and the hair follicles, Microsporum may also attack glabrous skin. M. canis (lanosum) has been isolated in several cases of dermatophytosis of the hands and feet. In the lesions can be seen mycelial filaments and small roundish spores from 2 to 3 microns in diameter, sometimes arranged in a mosaic pattern.

These organisms are easily cultivated on Sabouraud's or other sugar media. Sprouting, with branching mycelium and spore-bearing hyphae, may be observed. The hyphae show oval conidia from 3 to 4 microns long and from 2 to 3 microns wide, sessile or attached to short sterigmas. These conidia do not, as in the genus Trichophyton, appear *en grappe*. Terminal, septate, or nonseptate spindles, called *fuseaux*, and appearing as large fusiform structures from 30 to 60 microns long and from 15 to 18 microns wide, with granular contents, are present. At the apex can be seen peculiar hairlike formations (see definitions, p. 4). Chlamydospores usually make their appearance under unfavorable conditions, taking the form of large double-contoured cells, from 18 to 22 microns

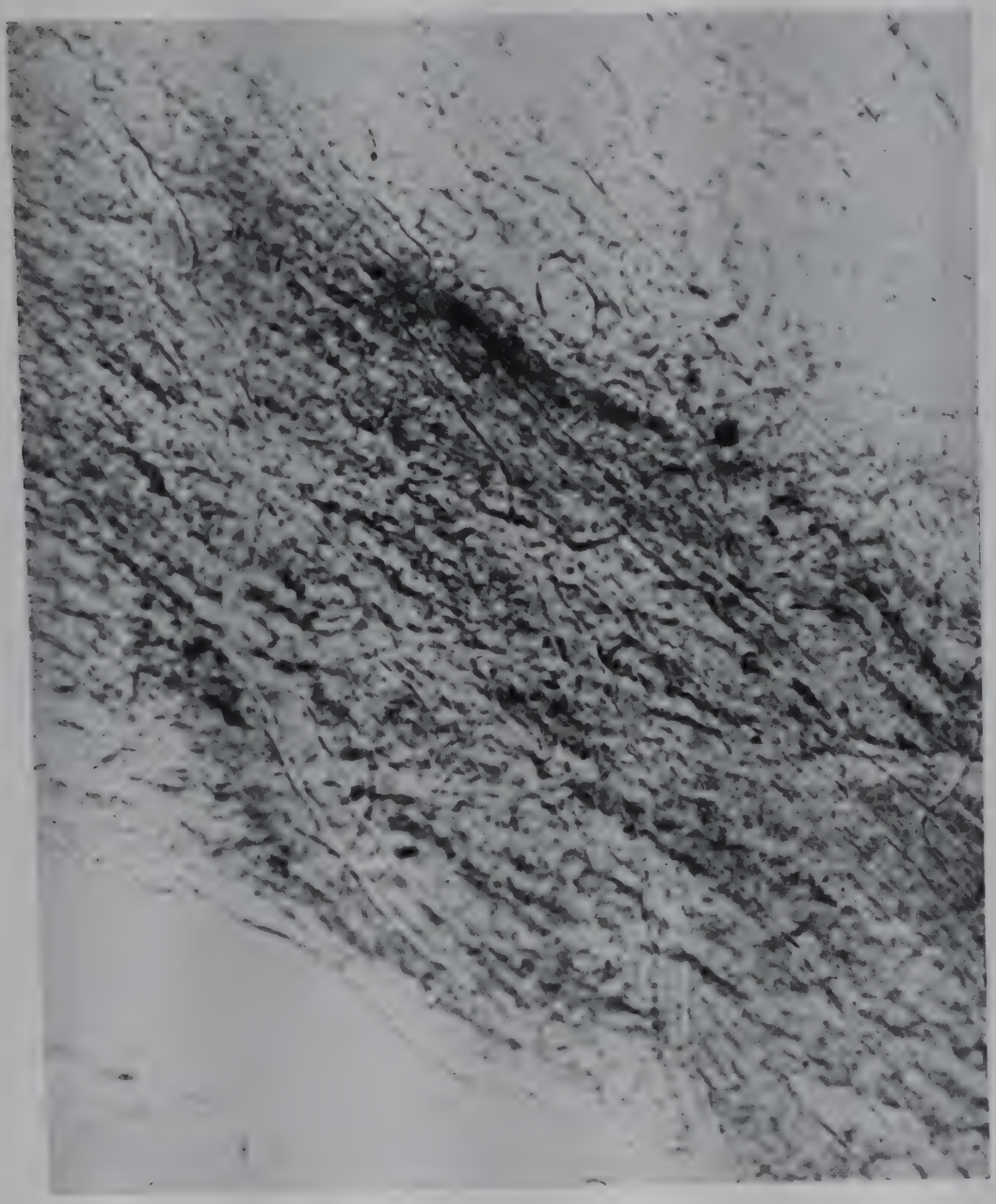

FIG. 29. SPORES AND MYCELIUM IN POTASSIUM HYDROXIDE PREPARATION OF HAIR IN TINEA CAPITIS

long and from 6 to 8 microns wide, that contain granular protoplasm. There are also denticulate or pectinate bodies—curved mycelial segments showing on the convex side several small protruding processes. *Pleomorphism*, the process by which a culture loses its distinctive characteristics and becomes unrecognizable, is more characteristic of the animal species

FIG. 30. HAIR INFECTED WITH MICROSPORUM, SHOWING SPORES. × 150

(i.e., M. canis, M. fulvum) than of the human species (M. audouini).

MICROSPORUM AUDOUINI (GRUBY, 1843)

On Sabouraud's dextrose medium, colonies are close and matted, showing after three weeks' growth some radiating furrows. On polished rice the only evidence of growth is a brownish discoloration of the medium. Conidiophores of varying lengths, simple at first and later occasionally showing a few branches, can be seen. Fuseaux vary in length from 31 to 82 microns and are anywhere from 8 to 14 microns wide;

the average length is 70 microns, the average width 12 microns. The shape of these tapers toward a slender outer end and a truncate base; their surfaces show numerous blunt-tipped spinous protrusions that under the microscope appear hyaline to light yellow. The microconidia are pyriform, measuring from 2 to 5 microns in length and from 1.5 to 2 microns in width;

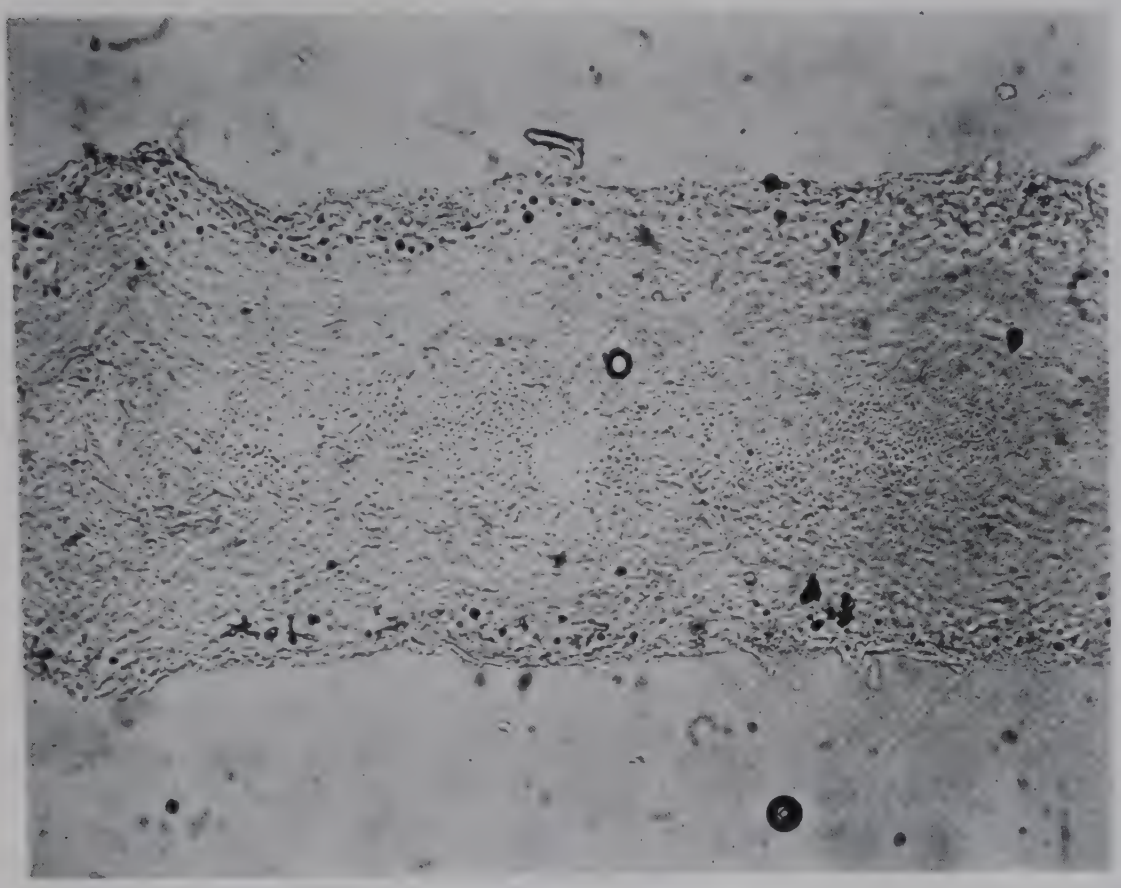

FIG. 31. SPORES AND MYCELIA IN POTASSIUM HYDROXIDE PREPARATION OF HAIR IN TINEA CAPITIS CAUSED BY MICROSPORUM. × 200

they are single-celled, sessile, or attached to short sterigmas, and pleurogenous. Nodular bodies in great numbers can be found inclosed in twisted, knotted hyphal strands. Pectinate hyphae are long, recurved, and locally expanded on the outer surfaces. Chlamydospores are borne both terminally and intercalarally in the submatrical hyphae. Racquet hyphae

are numerous everywhere. In the size and general characteristics of its fuseaux, this species closely resembles M. canis (lanosum).

On polished rice, no aerial mycelium is produced by M. audouini and, as already stated, growth is evident only as a progressive brownish discoloration of the medium, whereas an

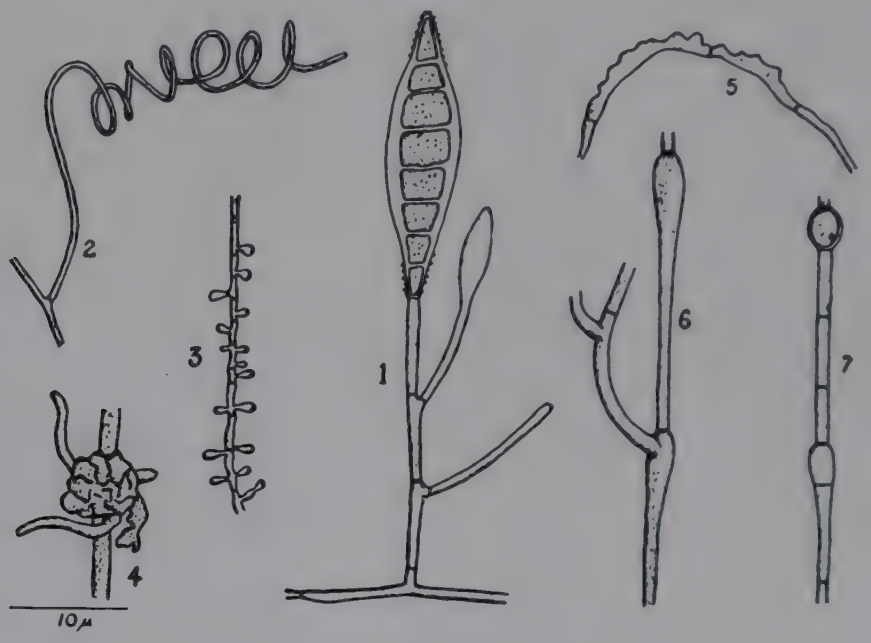

FIG. 32. REPRESENTATIVE STRUCTURES IN GENUS MICROSPORUM

1. Mature macroconidium (fuseau) seen in optical section (immature macroconidium begins as swelling at apex of side branch). 2. Spiral hyphae. 3. Laterally borne micronidia. 4. Nodular body. 5. Pectinate hypha. 6. Racquet hypha. 7. Chlamydospore, thick-walled resting spore. Spirals exceptionally rare.

abundant growth of aerial mycelium and numerous fuseaux characterize M. canis. Also, whereas M. audouini is clear and mouse gray throughout after ten days' growth on Sabouraud's medium, M. canis under the same circumstances appears under filtered ultraviolet rays to have a lavender-blue, shell-pink, or flesh-ochre center with a lavender-blue midzone (not always present), and an olive drab or mouse gray edge.

MICROSPORUM CANIS (BODIN, 1902)

Synonym: Microsporum lanosum (Sabouraud, 1907)

On Sabouraud's agar the growth at first differs from M. audouini only in its greater abundance and downiness. From twenty-five to thirty days after inoculation, the central portion becomes umbilicated, a ring of snow-white duvet surrounding the depression; in old cultures the ring may become yellowish. Microscopic examination shows spore-bearing hyphae with conidia from 3 to 4 microns long and from 2 to 3 microns wide and not supported by short sterigmas, in contrast with those of the genus Trichophyton. Fuseaux are found usually at the ends of certain filaments and measuring from 30 to 60 microns in length and from 15 to 18 microns in width; they are spindle-shaped, usually septate, and have granular contents. At the apex are some peculiar hairlike formations not observed in the spindle of Trichophyton. Chlamydospores, from 18 to 22 microns long and from 6 to 8 microns wide, with protoplasm that is usually granular and membrane that may be double-contoured, are generally found under poor conditions of growth. There are also denticulate or pectinate bodies, generally curved mycelial segments, with one side, usually the convex, showing small protruding processes.

Two-week-old colonies on rice are matted or cottony and white to pinkish buff, later becoming powdery with a pinkish buff to citron-yellow discoloration of the substratum. The conidiophores are at first simple and measure from 40 to 70 microns in length; the terminal conidiophores are more elongated and up to 190 microns long. Later these give rise by lateral ascending branching to shorter conidiophores that are hyaline and slender, swell gradually to the bases of the fuseaux, and sometimes reach dimensions of from 54 to 94 microns in length and from 14 to 22 microns in width. The microconidia are pyriform, sessile, or have short sterigmas, and have a length of from 3 to 5 microns and a width of from 1.5 to 2 microns.

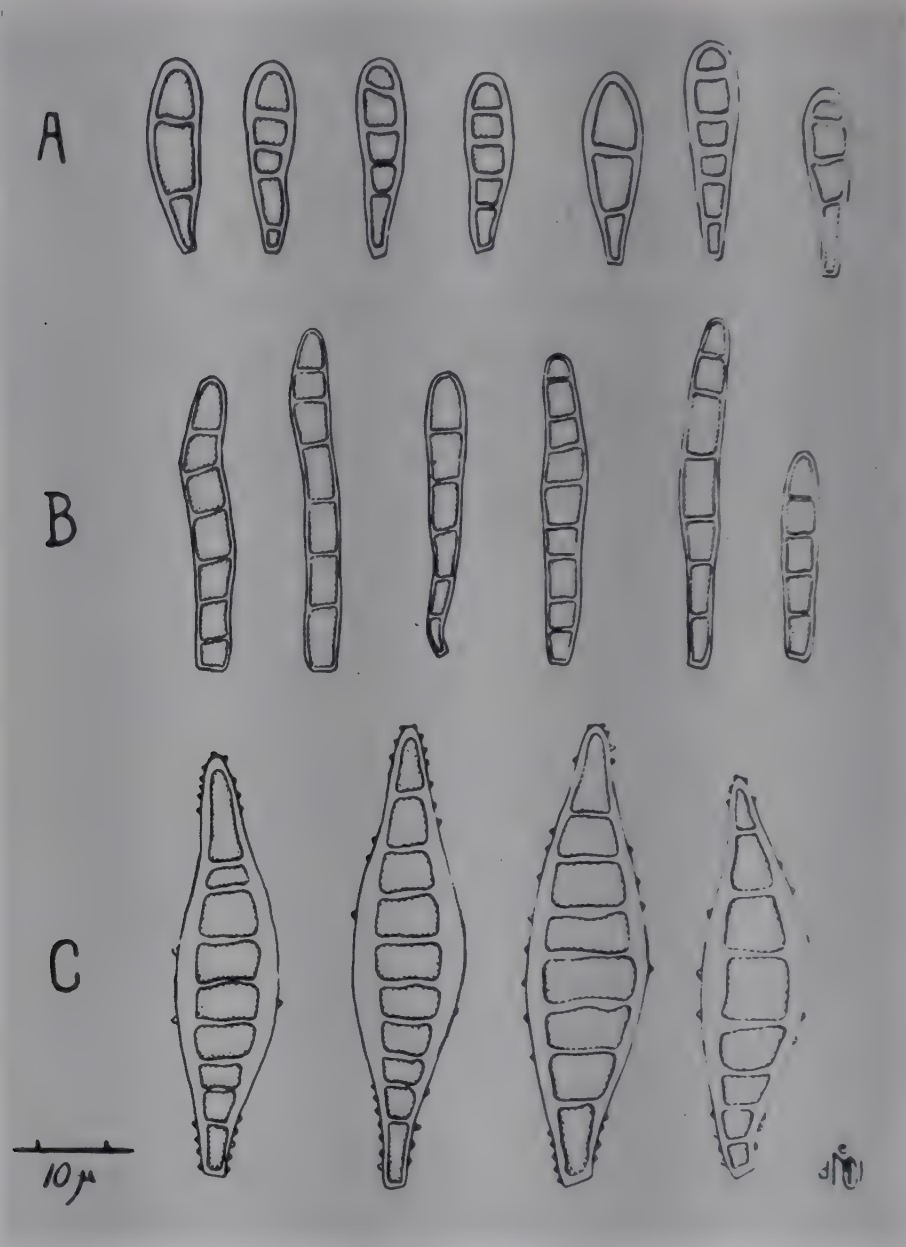

FIG. 33. TYPES OF FUSEAUX (MACROCONIDIA)

A. Club-shaped fuseaux of Epidermophyton
B. Long tapering fuseaux of Trichophyton
C. Thick-walled spindle-shaped multiseptate spiny fuseaux of Microsporum

Pectinate and spiralled hyphae are present, and racquet mycelium in abundance. This species differs from the others of the genus Microsporum in the extreme size of its fuseaux.

On Sabouraud's medium the 10-day-old culture appears under filtered ultraviolet rays to have a lavender-blue, shell-

FIG. 34. MICROSPORUM CANIS (LANOSUM)
Hanging-drop preparation showing fuseaux (macroconidia) at low magnification

pink, or flesh-ochre center, a lavender-blue midzone (not always present), and an olive drab or mouse gray edge.

MICROSPORUM GYPSEUM

Synonym: Microsporum fulvum

On Sabouraud's medium, the growth of this species is luxuriant and rapid. A central boss is seen, surrounded by a brownish powdery ring. The color may vary from cinnamon brown to a lighter shade of brown, almost to pink. An interest-

FIG. 35. MICROSPORUM CANIS (LANOSUM)
Culture mount showing spindle fuseaux (macroconidia). × 500

ing feature is the variation in color, to the point of complete loss of color in transplants of the same strain. White duvet covers the peripheral zone of the colony. Microscopically, truncate elongated fuseaux are seen, as well as pectinate hyphae and nodular bodies. On polished rice, the colonies at first show a white cottony growth, the mycelium later becoming

FIG. 36. MICROSPORUM FULVUM (Gypseum)
Culture mount showing fuseaux (macroconidia)

matted and powdery, with pale, ochraceous buff areas. The substratum is discolored to a pinkish buff. At first relatively simple, the conidiophores later become multibranched, the branches arising at right angles. The primary conidiophores may reach a length of 130 microns; the secondary conidiophores may be from 12 to 49 microns long and from 2 to 35 microns wide, becoming slightly expanded toward the apex. The fuseaux, which measure from 28 to 56 microns in length and from 8 to 14 microns in width, are elongate; their bases are ellipsoid and truncate. The fuseau wall is thin and the surface shows numerous wartlike projections. The microconidia, which are from 3.5 to 5.5 microns long and from 2 to 3.5 microns

wide, are sessile or grow on short slender sterigmas. Spiralled hyphae and chlamydospores are present.

Tinea Capitis

CLINICAL MANIFESTATIONS

Tinea capitis is caused by various species of fungous parasites, chiefly by the Microsporum group, sometimes by certain of the Trichophyton species—T. violaceum, T. crateriforme, T. gypseum, and T. sulfureum. Chiefly a disease of childhood, it rarely attacks adults. Microsporum canis (lanosum) and M. audouini are the two chief causative agents; the former is the most frequently encountered on the Atlantic seaboard.

Tables 1, 2, and 3 represent the incidence of species of Fungus and the sex incidence among 288 cases of tinea capitis in our series recently reported in the Archives of Dermatology and Syphilology.

Table 1.—*Incidence of Species of Fungus*

Species	No. of Cases	Percentage
Microsporum canis	188	65.3
Microsporum audouini	73	25.4
Microsporum fulvum	2	0.7
Trichophyton schoenleini	22	7.6
Trichophyton gypseum	2	0.7
Trichophyton sulfureum	1	0.3

Table 2.—*Distribution of Cases According to Sex (exclusive of favus)*

Sex	No. of Cases	Percentage
Males	165	62
Females	101	38

Table 3.—*Sex Incidence in Relation to Fungus Species in 256 Cases*

Sex	No. of Cases	M. audouini	M. canis
Male	156	55 (75%)	101 (55%)
Female	100	18 (25%)	82 (45%)

The clinical picture of tinea capitis and the course of the disease varies with the infecting micro-organism. Inflammatory reaction usually accompanies tinea capitis caused by M. canis,

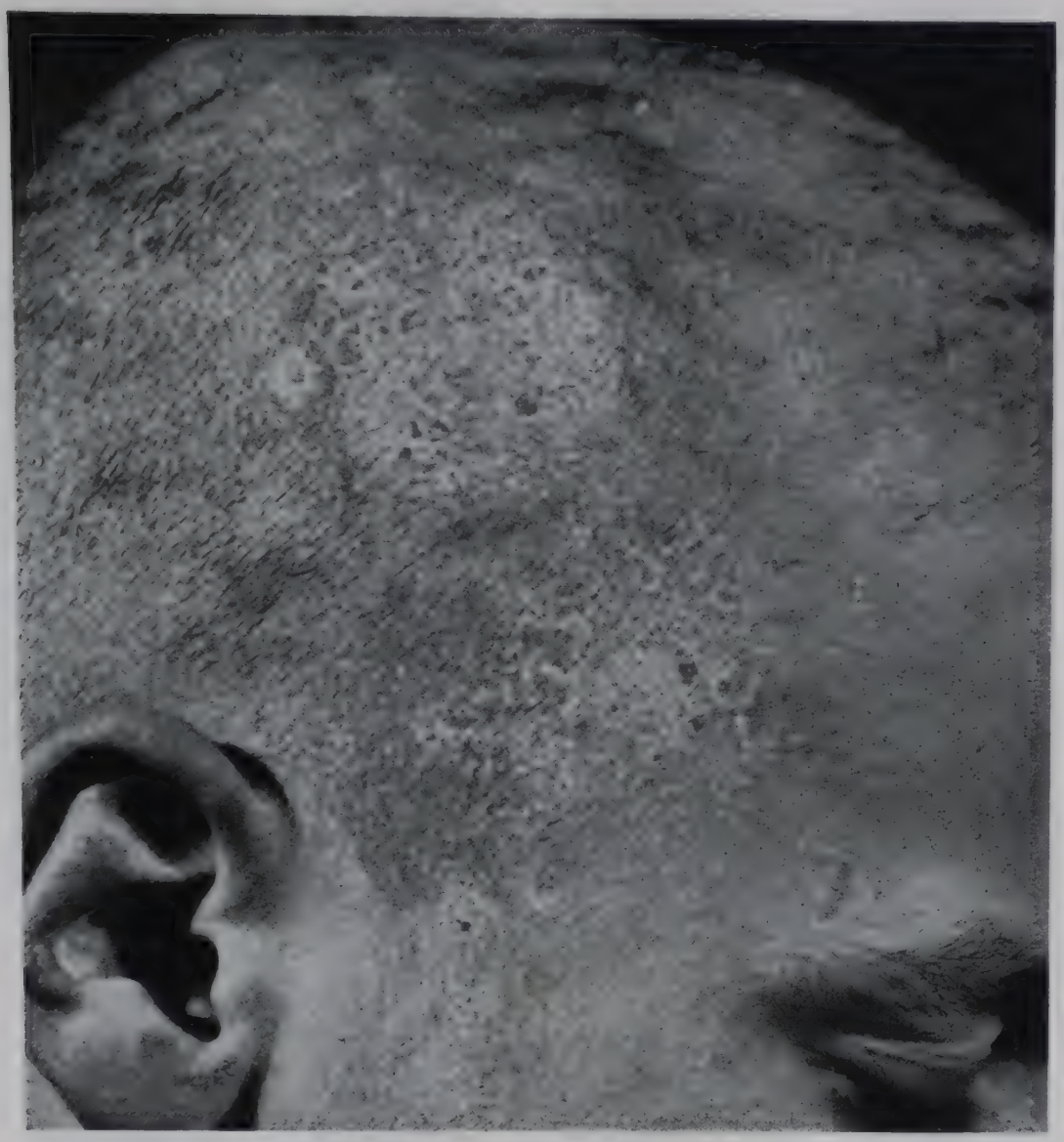

FIG. 37. TINEA CAPITIS CAUSED BY MICROSPORUM CANIS (LANOSUM)

M. fulvum, T. violaceum, T. crateriforme, T. gypseum, and T. sulfureum. Tinea capitis caused by M. audouini is usually noninflammatory in nature. The black-dot appearance is usually associated with T. violaceum.

Microsporum audouini. This micro-organism produces the noninflammatory type of ringworm of the scalp, commonly known as the "gray patch." The patches show broken-off dull hairs covered with a grayish sheath. The surface of the patch is usually scaly with little or no inflammation. The in-

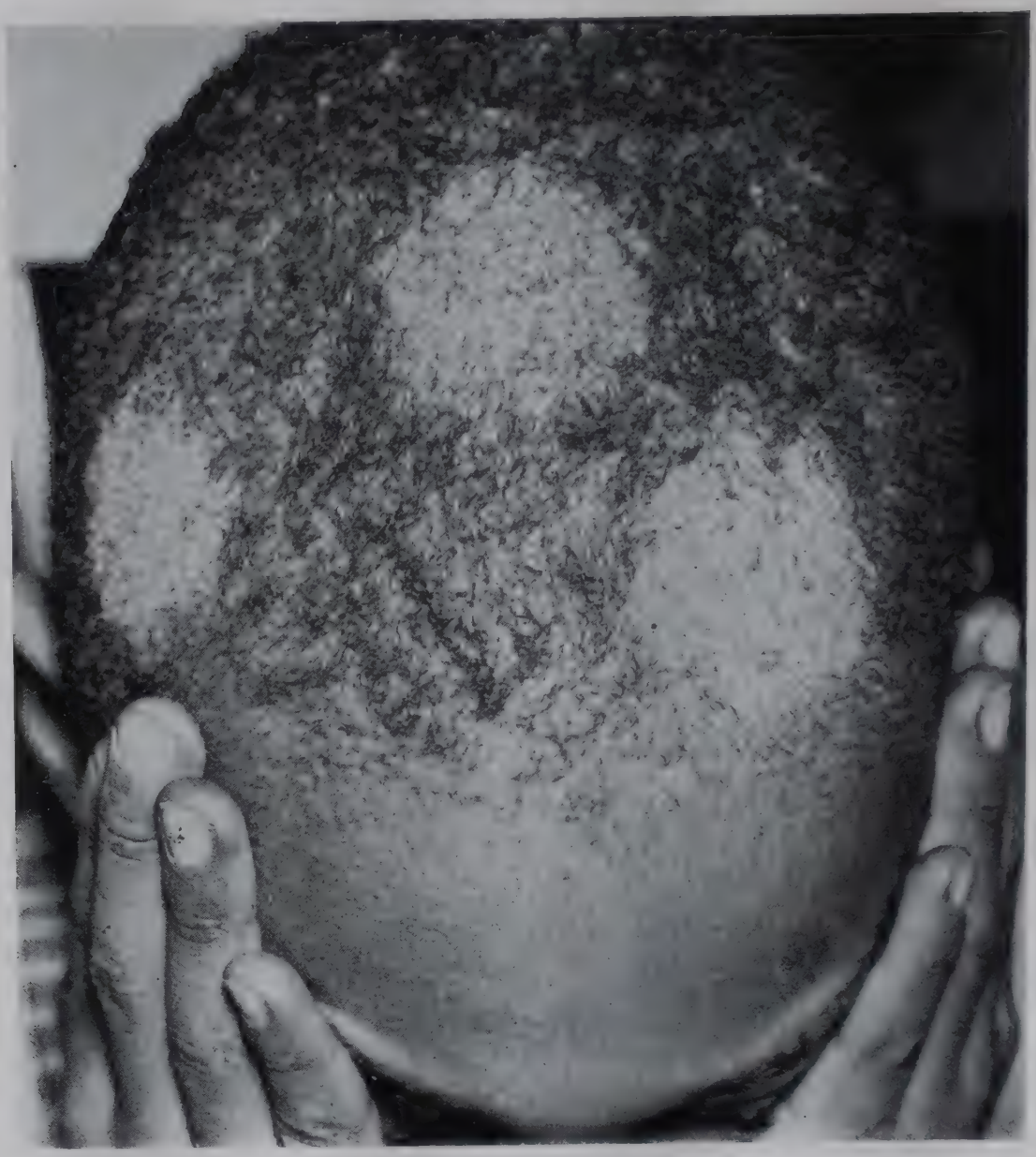

FIG .38. TINEA CAPITIS CAUSED BY MICROSPORUM AUDOUINI

fection usually begins as a small patch in the occipital and temporal regions. These patches enlarge in size and number to become scattered throughout the scalp. In general, the picture of extensive tinea capitis is that of a wheat field devastated by a tornado, with broken stalks bent or uprooted. There are rarely any lesions found on the glabrous skin either as a result of spread of the infection or cutaneous sensitization known as "id" reaction. Epidemics in orphanages and other institutions

FIG. 39. TINEA CAPITIS CAUSED BY MICROSPORUM FULVUM (GYPSEUM)

are common. Resistance to treatment is a common experience. The intracutaneous test with trichophytin shows either a slight or no reaction.

Microsporum canis (*lanosum*). As a rule, there is accompanying inflammation varying in degree. However, at times the clinical appearance of the patches in the scalp is indistinguishable from those in tinea capitis caused by M. audouini. Kerion formation occurs in about 3 to 5 per cent of cases. Glabrous skin involvement is common. Sensitization of the skin with resulting "id" eruption occurs. The intracutaneous test with trichophytin usually results in a moderate to vigorous reaction.

Microsporum gypseum (*fulvum*). The scalp lesion produced is usually inflammatory, and there is a tendency for the infec-

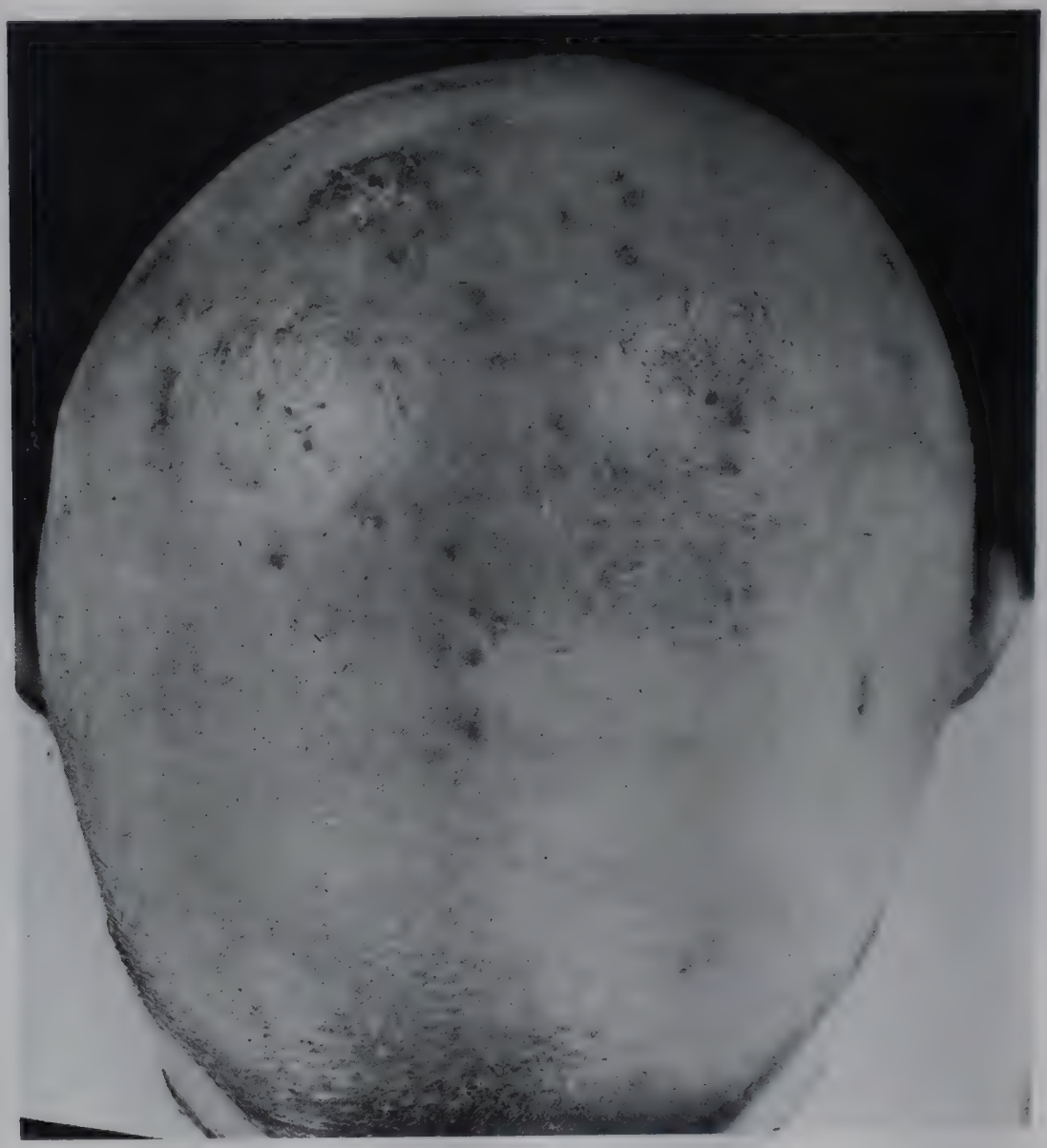

FIG. 40. TINEA CAPITIS AFTER X-RAY EPILATION

tion to remain localized. Kerion is common. Glabrous skin involvement is usual, producing typical lesions of tinea circinata with or without pustulation. Cutaneous sensitization with "id" reaction may be present. The reaction to an intracutaneous test with trichophytin is usually vigorous.

Hair stumps make the best material for microscopic study. These show the presence of the organism while scales usually do not. For direct microscopic examination, a few of the broken-off hairs are placed on a slide and a drop or two of 20

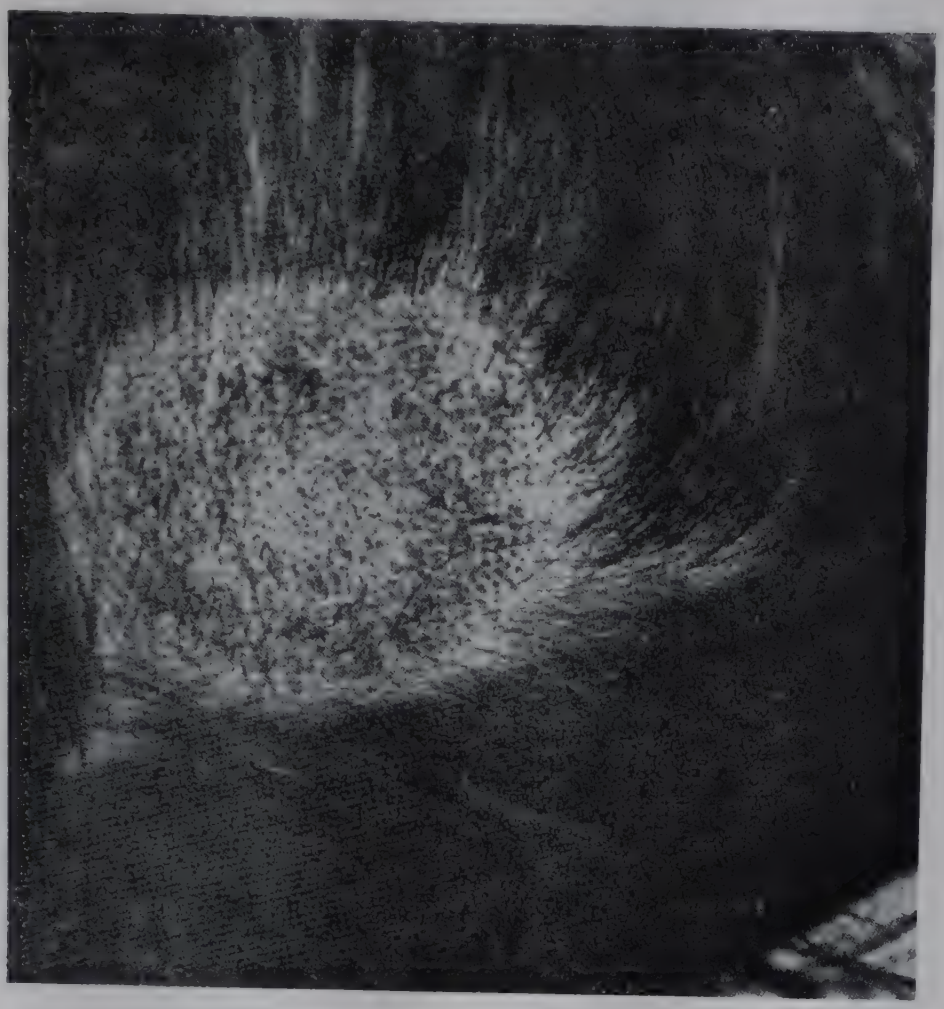

FIG. 41. TINEA CAPITIS CAUSED BY TRICHOPHYTON

to 40 per cent sodium or potassium hydroxide is added. The cover glass is then put in place, the preparation heated gently to the bubbling point, thinned by slight pressure on the cover glass, and allowed to stand for ten or fifteen minutes to clear. The microscopic field will reveal the presence of numerous small hyalin-like spores. Some of these, forced out by the pressure used in thinning the preparation, may be seen elsewhere than on the hairs. The field is best examined first with the low-power lens usually used for high-dry microscopic examination. Use of the Swartz-Conant stain or the counter stain (see pp. 16–17) is advised for a permanent preparation and for better study of the spore structure. For culture study some of the hairs should be planted on Sabouraud's

media. For cytologic studies, polished rice and other grain media may be used. To avoid pleomorphism and to preserve the culture for a long period, conservation media must be used (see p. 20).

Examination with a Wood filter for fluorescence aids in picking out infected hairs for microscopic examination (for technic, see p. 25).

Microsporid. As a result of cutaneous sensitization to the causative organism or to spread of its breakdown products by the hematogenous route from an inflammatory focus of the scalp, skin eruptions may appear. The eruption may be folliculo-papular, may simulate lichen scrofulosorum, may appear in groups of minute pustules or may be scaly. The eruption is usually found on the face, upper trunk, and extremities. The distribution is symmetrical. The lesions are void of fungi. Microsporid eruptions may be noted particularly following roentgen ray epilation or very active treatment. "Id" reaction is rare in noninflammatory lesions of the scalp and most commonly accompanies frank kerion.

Kerion Celsi

CLINICAL MANIFESTATIONS

This suppurative lesion, usually caused by M. lanosum, M. fulvum, T. violaceum, T. crateriforme, T. gypseum, has also been reported as caused by M. audouini. It is common in children.

The signs are loss of hair, inflammation, edema, bogginess, and a carbuncle-like tumor discharging a mucoid or mucopurulent secretion. Tenderness may be present but is usually absent. The size of the involved area may vary from that of a small bean to more than that of a walnut. Cutaneous sensitivity as manifested by an "id" reaction is frequently present. The trichophytin test usually shows a moderate to vigorous reaction except in cases of infection caused by T. violaceum when the reaction is negative.

Microscopically, the contents of the lesion or of the hairs within the infected area show the presence of various-sized spores and some branching hyphae. The lesion is sometimes mistaken for a carbuncle, but the latter condition is more painful and its existence is absolutely ruled out by the microscopic examination. The hair or the gelatinous fluid or both are

FIG. 42. KERION CELSI OF SCALP, CAUSED BY M. CANIS

placed on a slide, treated with 20 to 40 per cent sodium or potassium hydroxide, covered with a cover glass, heated gently to bubbling, thinned, and allowed to clear. In the fluid and hairs, numerous spores of varying size, with branching septate hyphae, are seen. The culture is prepared as in the case of tinea capitis.

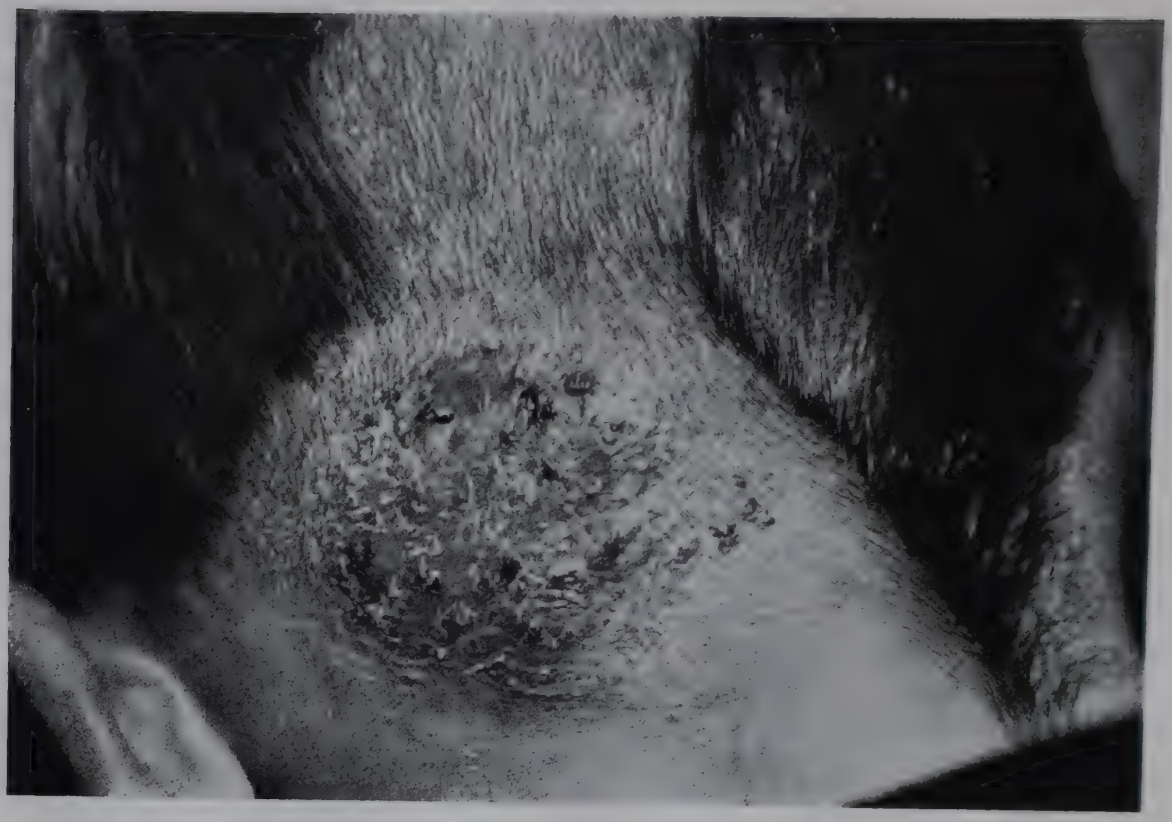

FIG. 43. KERION CELSI OF SCALP, CAUSED BY M. CANIS

TREATMENT

Treatment of tinea capitis depends a great deal upon the causative fungus. In general, infections caused by fungi which are also pathogenic to animals respond better to treatment, and often cure spontaneously. Infections caused by M. audouini and by the trichophyton (endothrix) are resistant to treatment and rarely cure spontaneously. Rothman and his co-workers demonstrated that the spontaneous cure of infections caused by M. audouini and the immunity of adult scalps are due to the presence in the sebum of adults of a higher concentration of saturated fatty acids with selective fungistatic and fungicidal action.

Since the infection is within the hair, treatment should be aimed at removal of infected hairs, either by manual or by roentgen ray epilation or by epilation with thallium acetate. For *manual epilation*, a forceps is used to pluck out the infected hairs or they are stripped out by means of adhesive tape. These measures are practicable only when the areas of involve-

ment are few and small, or when roentgen ray epilation is not possible. A demonstration by the doctor or nurse showing proper epilatory technic, and how to avoid spreading the infection by taking care to collect the hairs on some article that can be burned, is advisable. Epilation should be a daily procedure. One of the following fungicidal preparations should always be applied immediately afterward:

	Gm. or cc.
℞ Acidi salicylici	2.0
Sulphuris praecipitatis	2.0
Petrolati	30.0
ℿ	
℞ Phenolis	4.0
Camphoris	4.0
Iodini	4.0
ℿ	
℞ Sulphuris sublimatis	4.0
Phenolis	4.0
Naphtholis	2.0
Cerae albae	12.0
Adipis	20.0
ℿ	

Potassium permanganate solution (1 per cent) may be painted on twice a day. The child should wear a boilable inner cap that will cover the entire hairy region of the scalp, and this should be changed and boiled at least once a day. If the iodine solution produces a dermatitis, use of it should be suspended until the reaction disappears.

Sodium propionate solution may be applied mornings and sodium propionate ointment at night.

	Gm. or cc.
Sodium propionate*	12.3
Propionic acid	2.7

(*Continued on next page*)

* Sodium propionate solution, powder and ointment may be obtained from the Mycoloid Laboratories, Inc., Little Falls, New Jersey.

Sodium caprylate	10.0
Zinc caprylate	5.0
Dioctyl sodium sulfosuccinate	0.1
Carbowax 4000	69.9

Schwartz reports good results with the use of the following formulae in tinea capitis due to M. audouini.

	Gm. or cc.
1. Salicylanilide	5.0
Hyamine 1622 (25 per cent)	5.0
Carbowax 1500	100.0
2. S. S. copper undecylenate in carbowax 1,500	
3. Pentachlorophenol	1.0
Carbowax 1500	100.0

Roentgen ray epilation has proved very useful in the treatment of the resistant forms of tinea capitis. This method of treatment is a most delicate procedure, requiring considerable patience, special training, and skill. It can be dangerous in the hands of the inexperienced since the margin of safety between temporary and permanent epilation is narrow. It can be used only with patients old enough to remain absolutely still during treatment. The physician must make certain that no stimulating or irritating drug nor photo-active substance has been used for at least ten days prior to the exposure to the rays. The necessary local after-treatment may be initiated two weeks after irradiation. The reader is referred to Chapter XXVII in MacKee and Cipollaro's textbook, "X-rays and Radium in the Treatment of Diseases of the Skin," for the exact details on technic.

Thalium acetate is a highly toxic drug. A mistake in the dose of this drug may result in the death of the patient. Several reports of death due to the use of the drug have appeared in the literature. The authors do not recommend its use except in case of an epidemic in an institution for feeble-minded where epilation by x-ray is neither possible nor practical. Even in

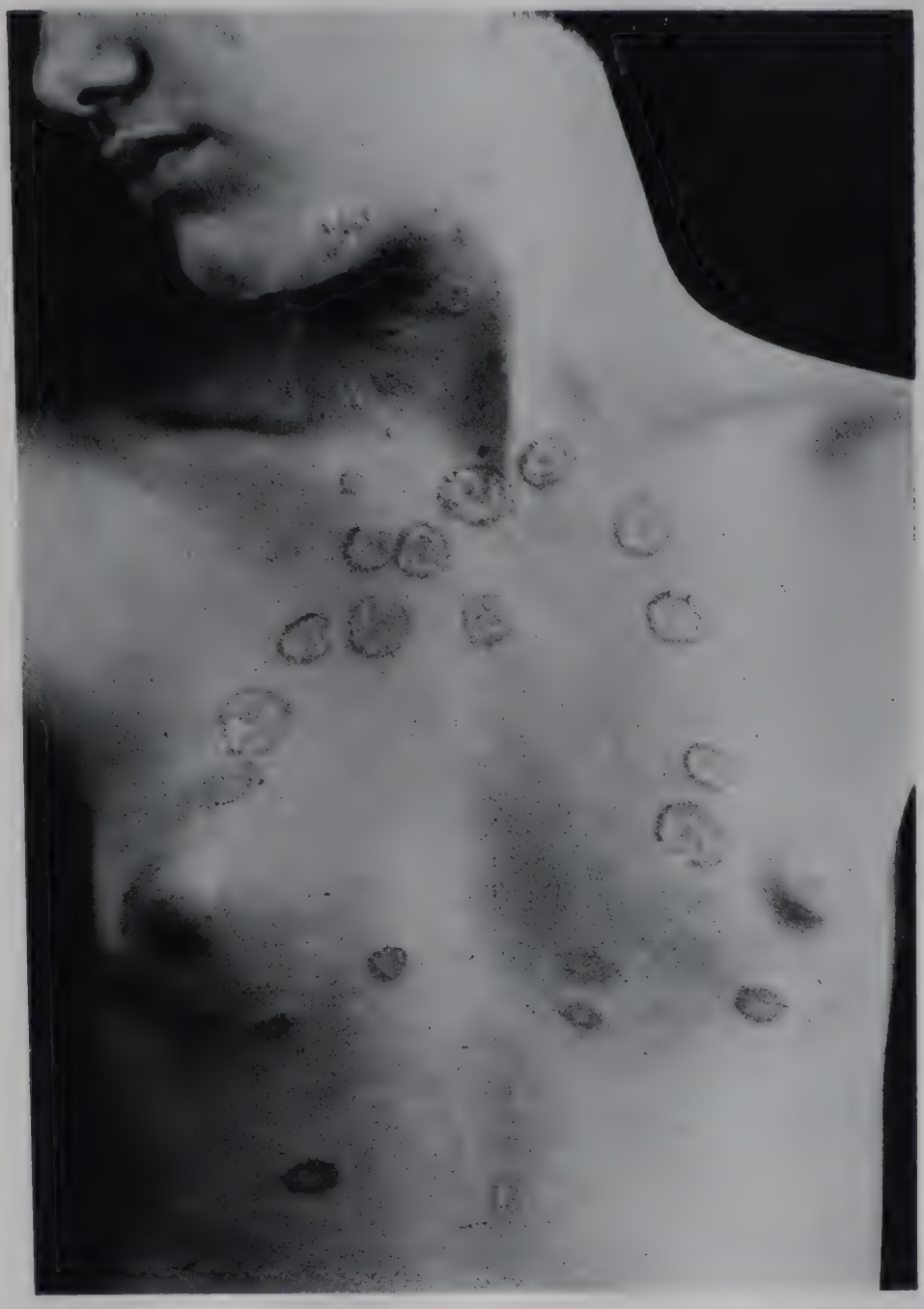

FIG. 44. TINEA CIRCINATA

such instances every other mode of therapy should be resorted to before thallium acetate is administered. Thallium acetate is contraindicated in patients with renal impairment. The drug is administered orally in a single dose of 8 mg. dissolved in sweetened water, per kilogram of body weight. The weight

FIG. 45. TINEA CIRCINATA

of both the child and the drug should always be rechecked by a competent person.

Ethyl iodide inhalations combined with local treatment and manual epilation may be used in cases in which the causative organism is M. audouini and in which x-ray epilation is not practical. At least three successive weekly negative examinations of the scalp under the filtered ultraviolet rays should be obtained before the patient is discharged as cured. Any questionable hairs should be checked by direct microscopic examina-

tion and cultural studies. The viability of the micro-organism in questionable hairs is best determined by cultural studies. A final inspection one month later is advisable.

TABLE 4.—*Cases Requiring X-Ray Epilation (exclusive of favus) in Our Series of 266 Cases*

Organism	No. of Cases	Percentage
M. canis	22	37.3
M. audouini	32	54.2
Trichophyton	1	1.7
Unidentified	4	6.8

TINEA CIRCINATA

CLINICAL MANIFESTATIONS

This disease may be caused by either the Microsporum or the Trichophyton family.

Tinea circinata is a superficial fungus infection characterized by the presence of superficial circinate lesions, with clearing centers. The border is composed of minute vesicles that soon dry up to form minute crusts and scales. At times there is formation of various figures, such as figures-of-eight or iris shaped lesions. The face, neck, and upper extremities are the most common locations, although any part may become involved.

This disease is sometimes confused with impetigo contagiosa and the herald spot of pityriasis rosea.

The presence of branching septate mycelia in the scales from the lesion when examined after being prepared with potassium hydroxide rules out the other possibilities.

TREATMENT

The sources of infection should be sought out—such as a pet animal or another child—and treated.

Local treatment consists of thorough cleansing, boiling of

clothing that comes in contact with infected areas, and application twice a day of 2 per cent gentian violet or the following ointment.

		Gm. or cc.
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0

℥

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CHAPTER V

GENUS TRICHOPHYTON

THE GENUS Trichophyton* includes a large number of species, some of them very rare. For the purposes of this text of condensed scope, only those most frequently encountered are singled out for discussion here. These include:

Trichophyton mentagrophytes (Robin; Blanchard, 1895)

Variants

Trichophyton gypseum
Trichophyton granulosum
Trichophyton asteroides
Trichophyton radiolatum
Trichophyton felineum
Trichophyton interdigitale
Trichophyton farinulentum
Trichophyton lacticolor
Trichophyton persicolor

Trichophyton rubrum (Castellani; Sabouraud, 1911)

Variant

Trichophyton purpureum (Bang)

Trichophyton megnini (Blanchard, 1895)

Variants

Trichophyton roseum
Trichophyton rosaceum

Trichophyton violaceum (Sabouraud, 1902)

Variants

Trichophyton violaceum
Trichophyton glabrum

Trichophyton tonsurans (Malmsten, 1845)

Variant

Trichophyton crateriforme

* In the terminology used in this chapter, the prefixes "ecto-," "mega-," "endo-," and "neoendo-," often used to qualify the term Trichophyton, have been omitted, since use of these merely complicates exposition.

FIG. 46. POTASSIUM HYDROXIDE PREPARATION OF SKIN SCALES, ROOFS OF VESICLES OR NAIL SCRAPINGS, SHOWING BRANCHING MYCELIUM. × 155

Trichophyton sabouraudi (Blanchard, 1895)

Variants

Trichophyton acuminatum Trichophyton pilosum

Trichophyton sulfureum (Sabouraud, 1910)

Trichophyton schoenleini (Langeron and Milochevitch, 1930)

Synonym

Achorion schoenleini

In hairy regions, characteristically the scalp or beard, this group of fungi produces ringworm. In glabrous skin, tinea circinata and dermatophytosis develop. Onychomycosis is another possibility. Although in some instances characteristic lesions are produced, it is not possible as a rule to make a diag-

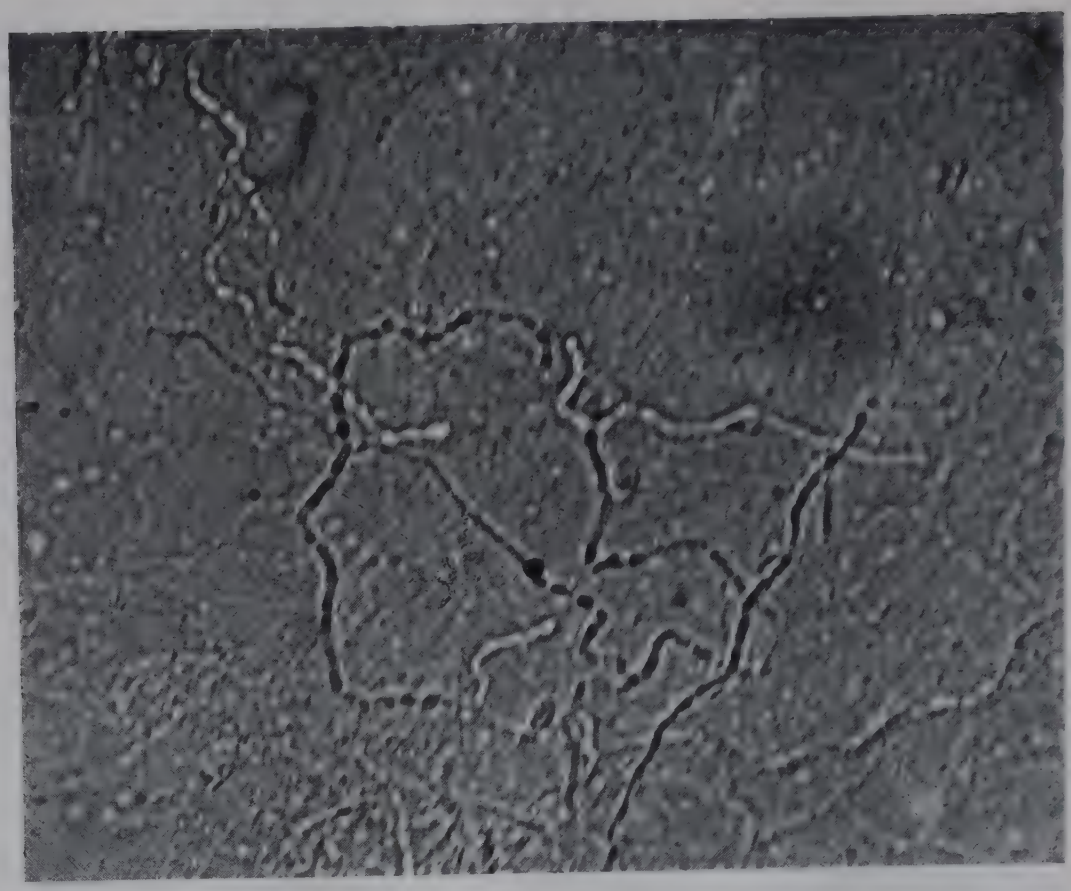

FIG. 47. DIRECT MICROSCOPIC EXAMINATION OF SKIN SCALES, ROOFS OF VESICLES AND NAIL SCRAPINGS, SHOWING SEPTATE AND NONSEPTATE MYCELIUM. × 500

nosis of the fungus species concerned on the basis of the clinical findings; cultural and morphologic studies are necessary.

The organisms are easily cultivated on Sabouraud's medium or other sugar media. The culture shows branching mycelium, spore-bearing hyphae, conidia attached singly or appearing *en grappe*, and multiseptate tapering thin-walled fuseaux (macroconidia). The last-named are usually found less frequently than in the genus Microsporum and sometimes require special media, such as polished rice or other grain media, to bring them out. Spirals are present, particularly in T. gypseum. Unfavorable conditions usually give rise to chlamydospores.

TRICHOPHYTON GYPSEUM (BODIN, 1902)

This species includes most of the kerion-producing organisms

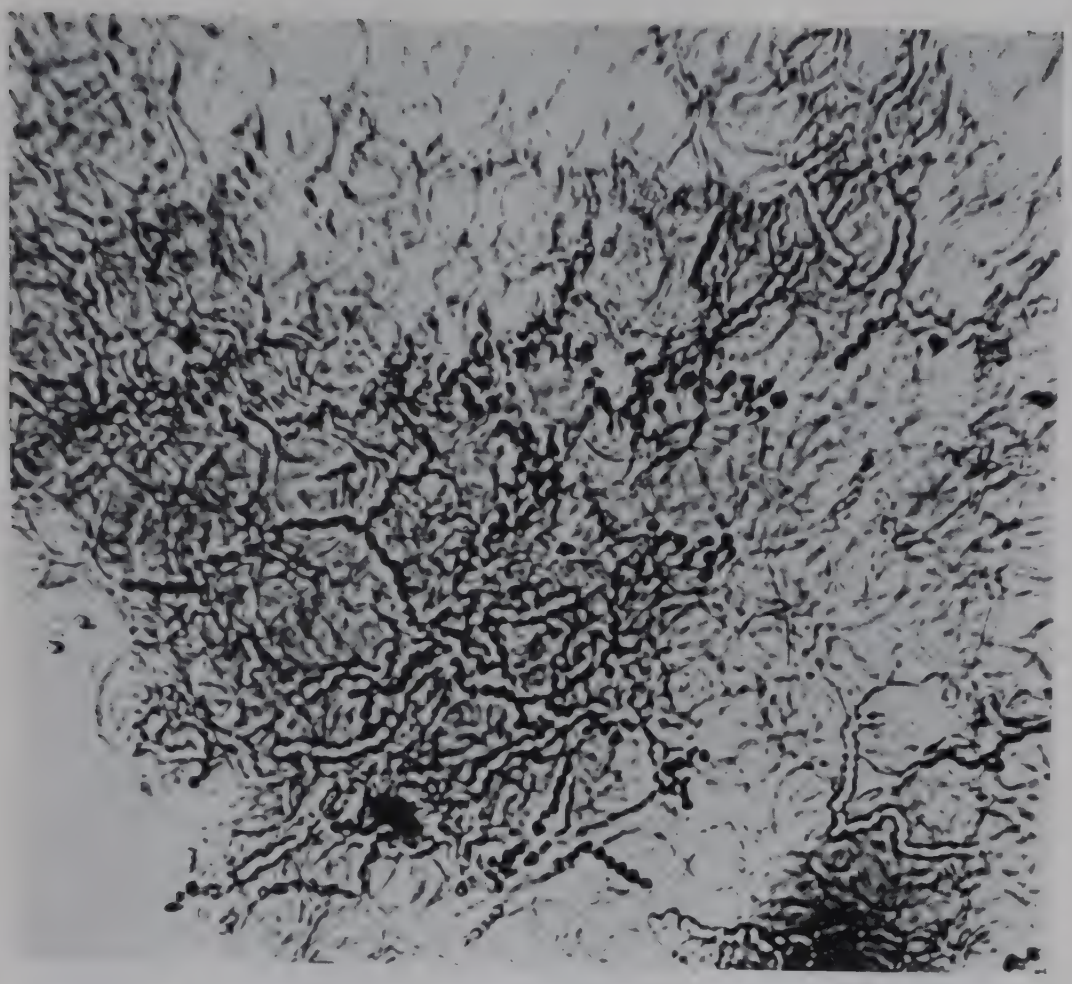

FIG. 48. LOW POWER PREPARATION DEMONSTRATING BEADED SEPTATE MYCELIUM IN SCALES FROM DERMATOMYCOSIS
Lactophenol-cotton blue stain. × 400

and many of those causing sycosis and dermatophytosis. The parasite is common in the United States, among French, German, and Hungarian agricultural laborers, but has been found also in São Paulo, Brazil, in Uruguay, in Tomsk, Siberia, and in Japan. It is one of the chief fungi causing dermatophytosis of the feet, intertrigenous infections, and infections of the nails. It has been found on horses and is pathogenic in guinea pigs.

MYCOLOGY

The organism can be recovered from lesions of the glabrous skin, scalp, and beard. Growth is rapid. Colonies are characteristically powdery; in rare instances they are velvety. The

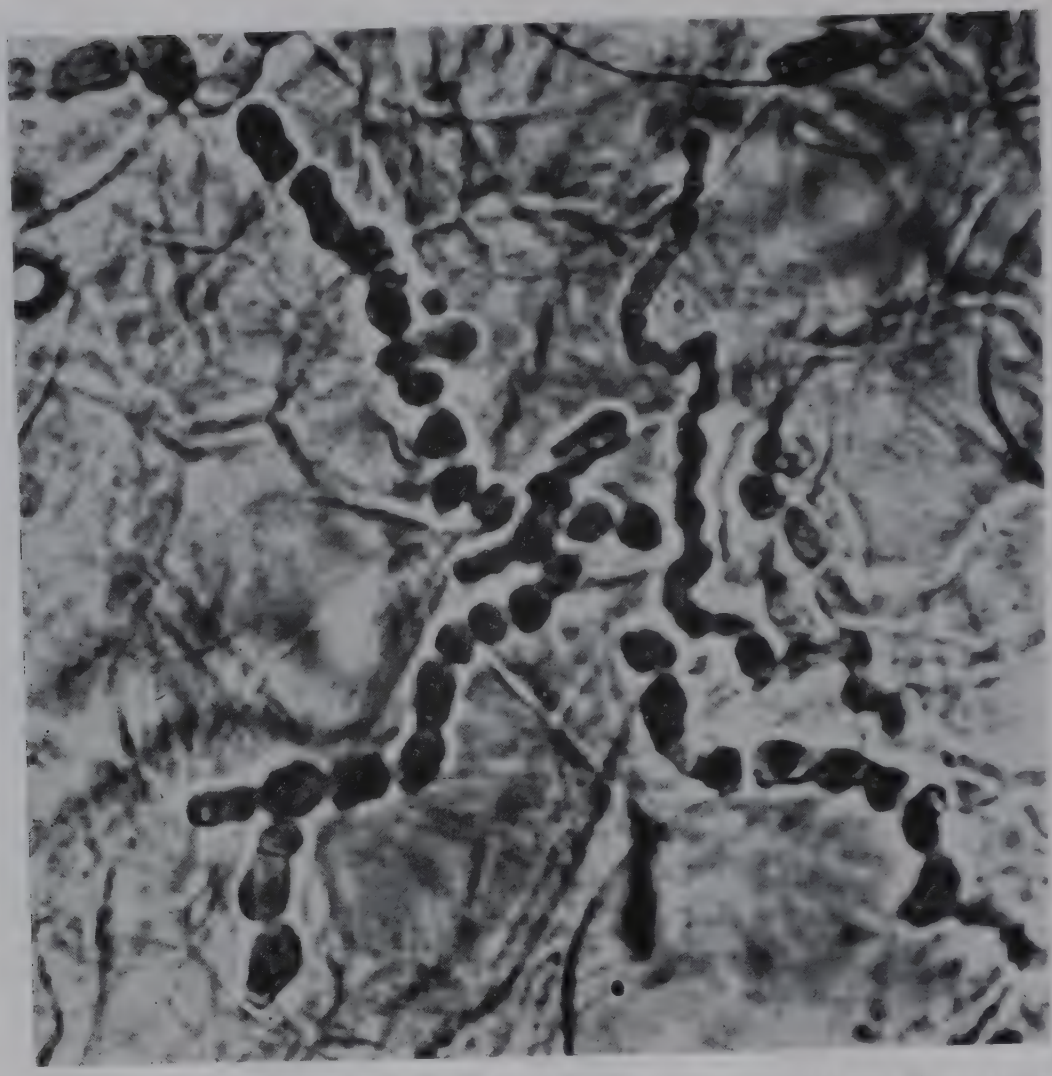

FIG. 49. MYCELIA IN SCALES FROM DERMATOMYCOSIS. STAINED PREPARATION. × 700

central, deeply furrowed cupola, with rudimentary, spearlike rays and a white powdery disk, is distinctive. On Sabouraud's glucose agar, the round, domed center, marked by powdery rays, later becomes umbilicate, with multiplying lanceolate rays that appear to be dusted with a white powder where they reach the surface of the medium. The reverse side of the medium is reddish in color. Pleomorphism occurs in four or five weeks. On Sabouraud's conservation agar, the surface resembles irregular lunar craters and appears powdered, though more lightly, as on carbohydrate media.

Cutaneous sensitivity with resulting "id" reaction does occur.

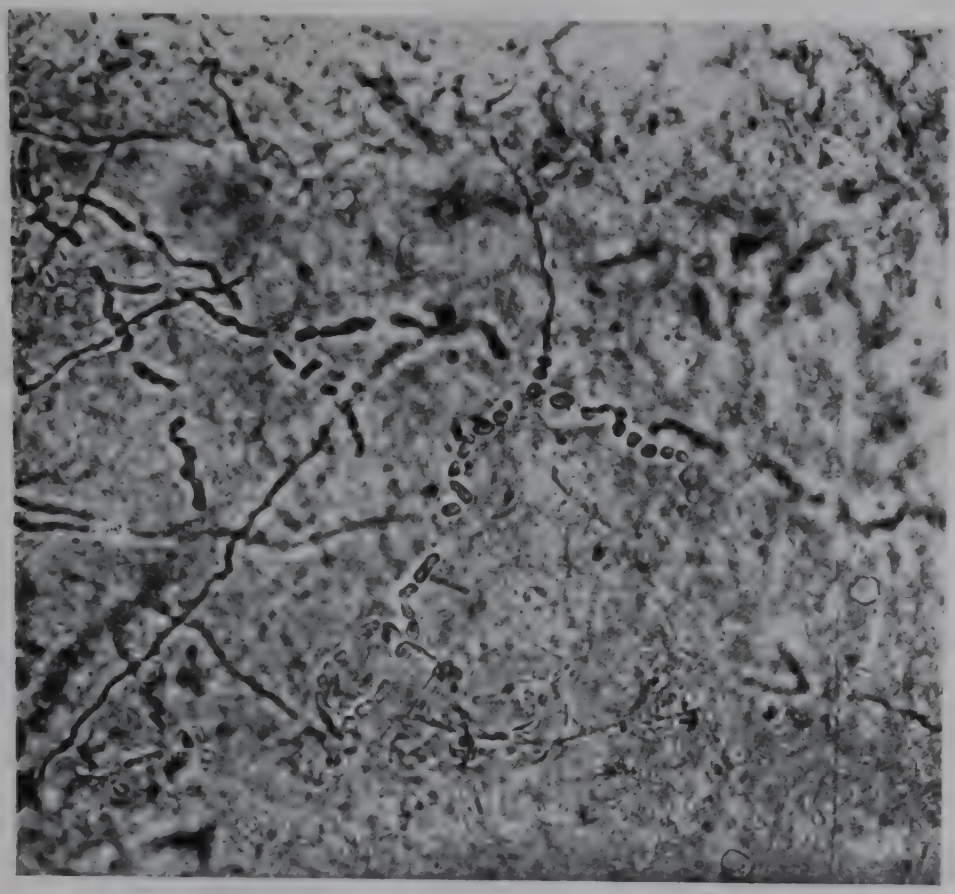

FIG. 50. ACTIVE AND DEGENERATED MYCELIUM; POTASSIUM HYDROXIDE PREPARATION OF SKIN SCALES, ROOFS OF VESICLES OR NAIL SCRAPINGS. × 500

A reaction to an intracutaneous test with trichophytin can be elicited. Lewis and Hopper feel that the powdery type sensitizes the skin to a greater degree than the fluffy type.

TRICHOPHYTON INTERDIGITALE

This micro-organism is considered to be a variant of T. gypseum and causes intertrigenous infections of the feet. It is common in Austria, Germany, United States, Spain, Argentina, São Paulo, and Brazil.

MYCOLOGY

On Sabouraud's agar the rate of growth is fast, beginning as a downy feather-like projection and within two weeks almost covers the entire agar slant as a white fluffy growth. On

culture mount vegetative filaments, microconidia en grappe, nodular bodies and racquet mycelium are found. Spirals and fuseaux are difficult to demonstrate. The fuseaux may be demonstrated when grown on grain media, particularly rice.

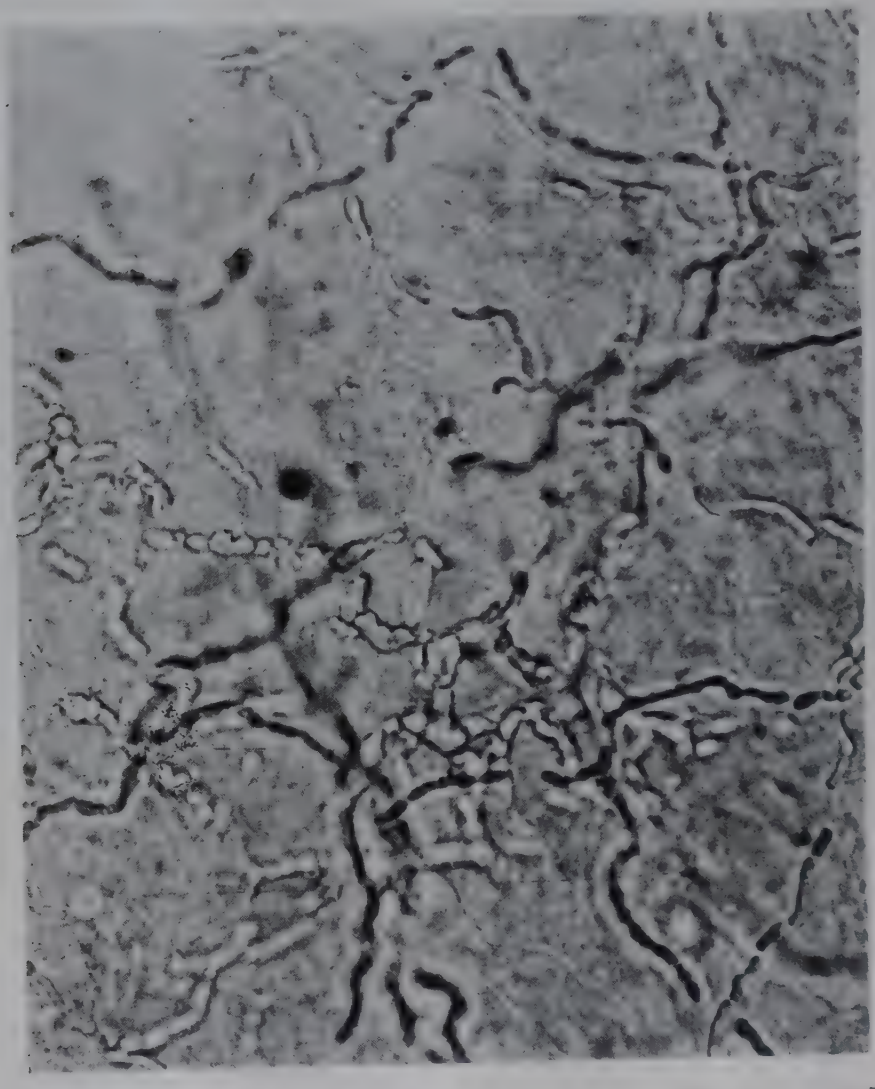

FIG. 51. MYCELIA AND MOSAIC STRUCTURE IN SCALES. × 500

TRICHOPHYTON GRANULOSUM

This organism is looked upon as a varient of T. gypseum. A cause of scalp kerion and beard ringworm, T. granulosum, has been reported from Poland, Manchuria, Japan, and São Paulo, Brazil.

MYCOLOGY

On Sabouraud's agar, the colony is powdery and shows a yellowish white disk with a scattering of granules, its center having a raised crater or radial folds that are sometimes half-hooded. On conservation agar the central portion is smaller, the denticulate margin larger, and the surface often dewy.

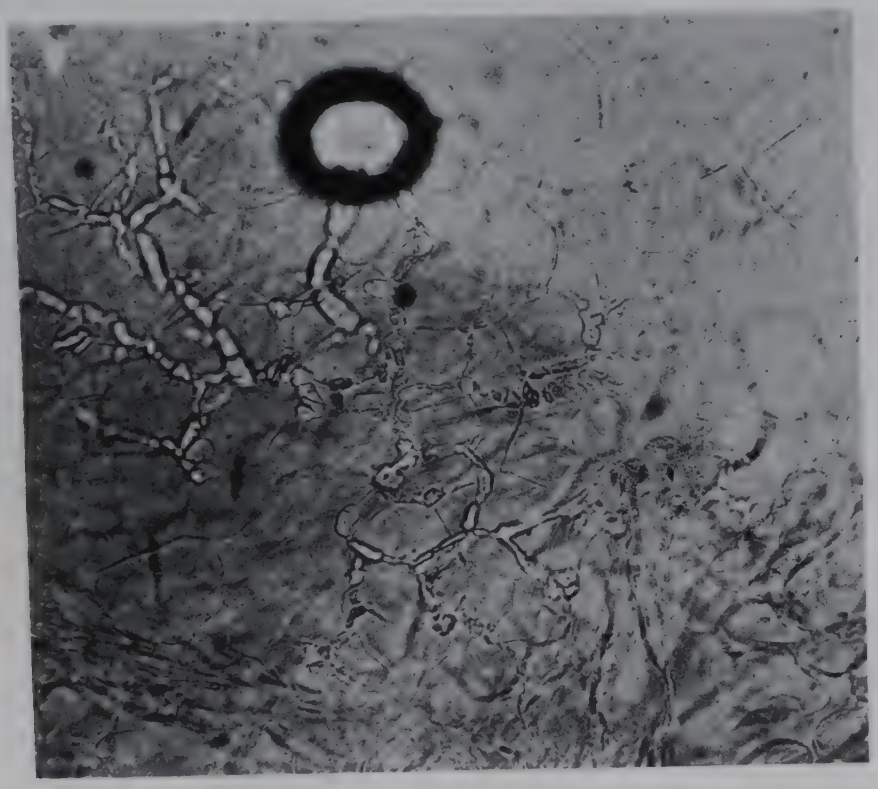

FIG. 52. MOSAIC STRUCTURES. × 500

TRICHOPHYTON FELINEUM

Probably a variant of T. gypseum, this organism attacks chiefly glabrous skin. It is reported from France, Germany, Switzerland, Austria, and Japan.

MYCOLOGY

Cultures on Sabouraud's glucose or maltose agar produce a pure white, velvety colony having a crater-like center from

FIG. 53. ARTEFACTS. POTASSIUM HYDROXIDE CRYSTALS. × 200

which long slender delicate rays fan out. Pleomorphism does not occur.

TRICHOPHYTON LACTICOLOR

A cause of tinea sycosis, this organism has been reported from France, Germany, Sweden, Hungary, Japan, from São Paulo in Brazil, and from the state of New York.

MYCOLOGY

On culture, the butter-colored colonies show flat disks cut by shallow radial grooves. The surface suggests hot curdled milk. On conservation media, the colony takes the shape of a truncated cone, with furrows spreading from an extremely deep central depression. The surface is velvety.

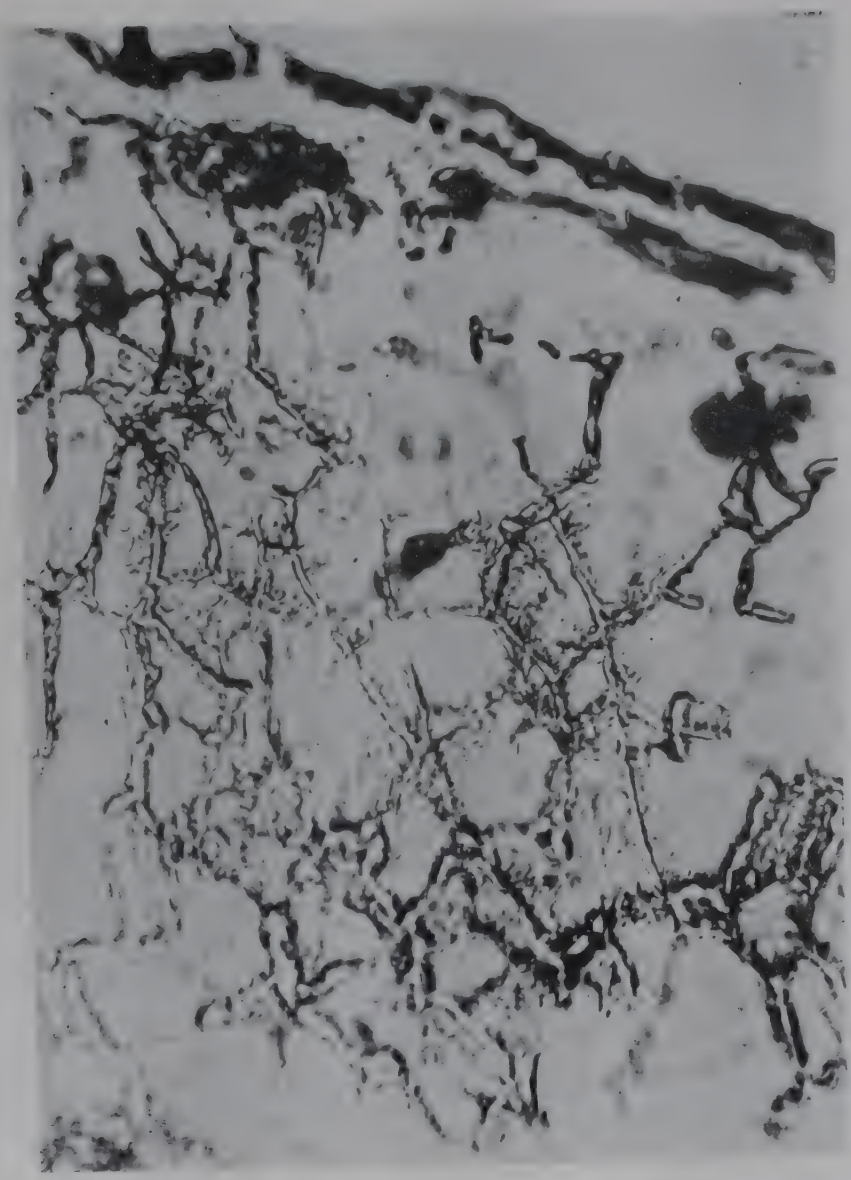

FIG. 54. ARTEFACTS PRODUCED BY GLYCERIN AND POTASSIUM HYDROXIDE, SIMULATING MOSAIC STRUCTURES. × 400

TRICHOPHYTON RUBRUM

This organism attacks glabrous skin chiefly, but it has been found in lesions of onychomycosis and tinea sycosis as well. Ota has disclosed it to be a frequent cause of tinea cruris in Japan and Manchuria. Weidman states that it is common in the South, where cases diagnosed as eczema marginatum, onychomycosis, and dermatitis were shown by Hodges to be actually due to T. rubrum. Lewis, Montgomery, and Hopper

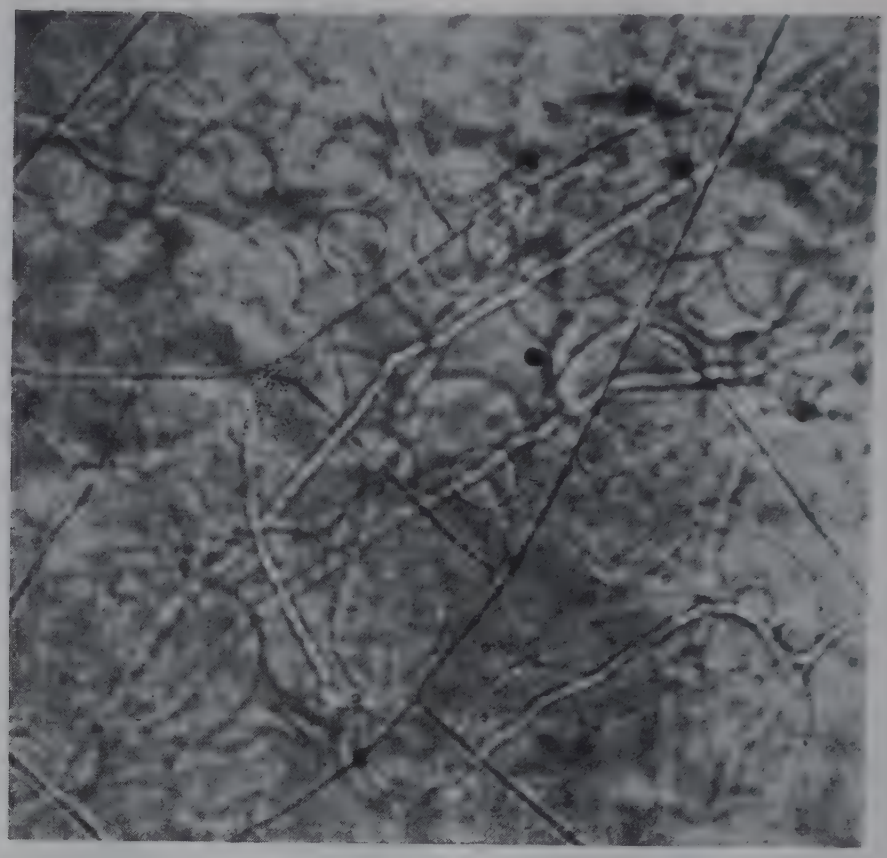

FIG. 55. MYCELIUM AND LINEAR CRACKS IN COVER SLIP. × 500

found this parasite in dermatoses simulating arsenical keratosis, neurodermatitis, eczema, sycosis vulgaris, and erythema annulare centrifugum. The author (J. H. S.) and Conant reported 4 cases of extensive lichenified dermatitis due to T. rubrum.

MYCOLOGY

On Sabouraud's dextrose agar, growth begins in from four to six days. In about seven days, a reddish purple pigmentation appears, this being especially noticeable on the reverse side. After ten days there develops in the center of the colony an aerial mycelium, which gives way to a powdery type of growth. At first white, it deepens to pink in the 3-week-old culture. In subcultures the purplish hue tends to fade out.

Microscopic examination reveals the presence of aleurospores, both single and clustered, chlamydospores, fuseaux (macroconidia), spirals, and an occasional nodular body.

FIG. 56. SPIRALS IN T. GYPSEUM (HANGING-DROP PREPARATION). × 700

Cutaneous sensitivity with resulting "id" reaction is rare. A reaction to an intracutaneous test with trichophytin is usually slight or absent.

TRICHOPHYTON MEGNINI (BLANCHARD, 1895)

Variants: Trichophyton roseum (Bodin); Trichophyton rosaceum (Sabouraud)

This species causes tinea of the beard in man and attacks animals as well. It is common in the north of England and endemic in France, Belgium, the Netherlands, Denmark, and

FIG. 57. SPIRALS IN CULTURE MOUNT OF T. GYPSEUM. × 500

Germany. It is occasionally encountered in Italy, and on the American continent in the cities of Montreal and Philadelphia. It is seen, rarely, in Japan and São Paulo, Brazil. It is transmissible to guinea pigs and dogs.

MYCOLOGY

On culture, the colony gradually changes in color from a velvety pure white to pale rose, with the reverse side taking on a gooseberry violet hue. On Sabouraud's conservation agar, the surface is snow white and the underside black. Pleomorphism occurs.

TRICHOPHYTON VIOLACEUM (SABOURAUD APUD BODIN, 1902)

Producing tinea capitis, tinea circinata, onychomycosis, and sycosis, this organism is found in Russia, Poland, and

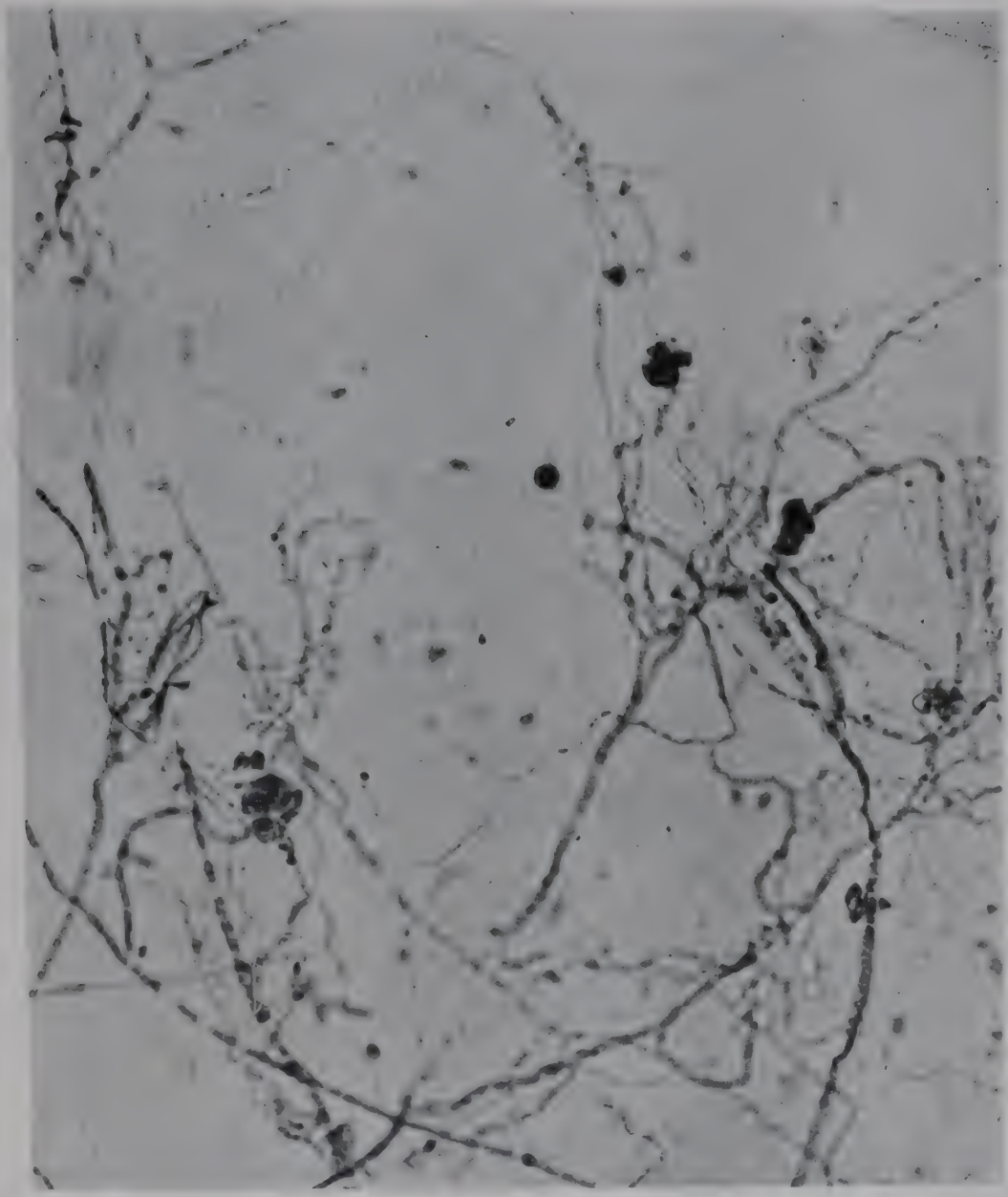

FIG. 58. NODULAR BODIES IN CULTURE MOUNT FROM GENUS TRICHOPHYTON. × 500

France, and has been reported in regions from Palestine to Algeria and parts of the Sudan. In the United States the organism is chiefly found in immigrants. Only sporadic cases have been noted in American born. It is inoculable in guinea pigs, dogs, and cats.

MYCOLOGY

The colony fades from an initial violet to grayish white and

FIG. 59. RACQUET MYCELIUM IN CULTURE MOUNT FROM GENUS TRICHOPHYTON. × 500

becomes powdery or chalky at the periphery as it ages. It is rounded, often having a small central protuberance; five or six radial folds can be seen. Pleomorphism is not common. Microscopically, only mycelium and chlamydospores are seen.

Cutaneous sensitivity with resulting "id" reaction is rare. The reaction to an intracutaneous test with trichophytin is usually slight or absent.

Trichophyton Tonsurans (Malmsten, 1845)

Variant: Trichophyton crateriforme

This organism produces tinea capitis, and is the most common species of Trichophyton found in the city of Paris; it is widespread in western Europe. It is inoculable in guinea pigs.

MYCOLOGY

The colony is white and velvety, with a yellowish buttony center, being crateriform in shape. Later it becomes powdery. Pleomorphism is not common. Microscopically one sees aleurospores that may appear both laterally and in thyrses and show hyphal tips that are often clavate; these aleurospores are sometimes sessile. Transitional forms ranging down to small chlamydospores may be seen.

The reaction to an intracutaneous test with trichophytin elicits a vigorous response.

Trichophyton Sabouraudi

Variant: Trichophyton acuminatum

This organism, which causes tinea capitis, is widespread in Europe. It is inoculable in guinea pigs.

MYCOLOGY

As the colony ages it changes from a small hemispherical mass to a white, then creamy, finally brownish and sometimes violet-tinted flattened cone that has furrows of varying depth radiating from the center, and a thin flat margin. Pleomorphism is rare. Microscopically, one finds lateral or grouped aleurospores and swellings on the hyphae that suggest young chlamydospores.

Trichophyton Sulfureum (Sabouraud, 1910)

This is common in England and Australia, producing tinea capitis and lesions on glabrous skin.

MYCOLOGY

The colony at first shows a velvety surface, which later becomes roughened and irregular. The color varies from a delicate to a sulfur yellow.

Trichophyton Cerebriforme (Sabouraud, 1910)

This is probably a variant of T. sulfureum (Sabouraud, 1910). This organism causes tinea barbae and, rarely, tinea capitis. It is common in England, France, Italy, and Germany.

Fig. 60. Tapering Fuseaux (Macroconidia) and Conidia en Grappe in Culture Mount of Genus Trichophyton. × 500

MYCOLOGY

At first white and having a crater that disappears as the folds become prominent, the cerebriform surface deepens to

cream and finally takes on a yellowish hue at the center. Distinct and unequal marginal rays are seen on the crackled surface. Microscopically one sees terminal and intercalary chlamydospores, lateral aleurospores, and abundant arthrospores.

FIG. 61. EARLY SPORULATION IN GENUS TRICHOPHYTON. × 500

TRICHOPHYTON SCHOENLEINI (LANGERON AND MILOCHEVITCH, 1930)

Synonym: Achorion schoenleini

The organism causes tinea favosa and is pathogenic in man, guinea pigs, rats, mice, cats, and rabbits. Except in the case of rats, it very rarely occurs spontaneously in these animals. T. schoenleini is common in southern Japan, Algeria, Holland,

the Rhine Valley, and in eastern Germany, especially in Silesia; it occurs also in Bosnia, Hungary, Poland, the Russian border states, in Transcaucasia, Bessarabia, Italy, Scotland, and occasionally in France. It occurs, only rarely, in Formosa, northern Japan, Manchuria, the United States, Portugal, Argentina, and in São Paulo, Brazil.

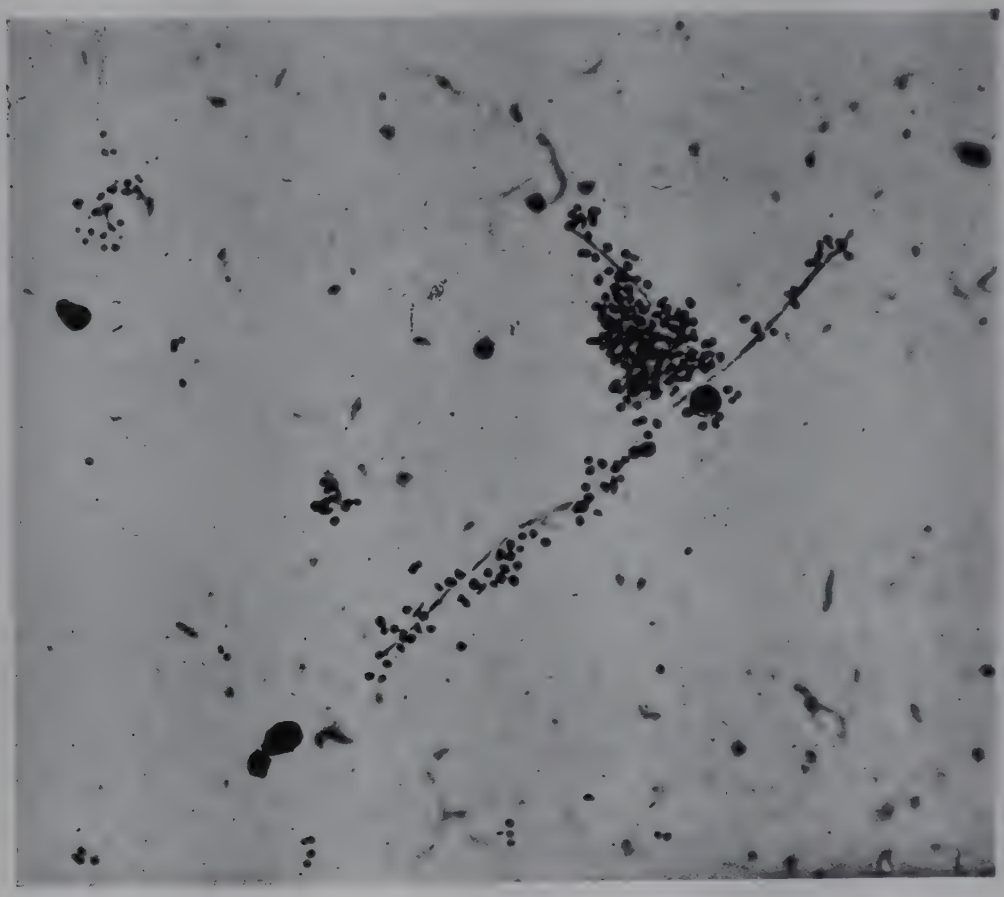

FIG. 62. CONIDIA EN GRAPPE IN CULTURE MOUNT OF GENUS TRICHOPHYTON. × 500

MYCOLOGY

The yellowish scales or crusts or the hair, or both, provide the best material for microscopic examination. This is placed on a slide, treated with 20 to 40 per cent sodium or potassium hydroxide, heated to bubbling, thinned, and cleared. The microscopic field shows spores of varying size and shape. Particularly typical is the sausage-shaped spore. Hyphae are septate

and rather coarse. In some fields the organism may be missing, but vestigial traces can be found in the hairs.

On Sabouraud's dextrose agar, the rate of growth is usually slow. About three weeks are required to obtain a recognizably

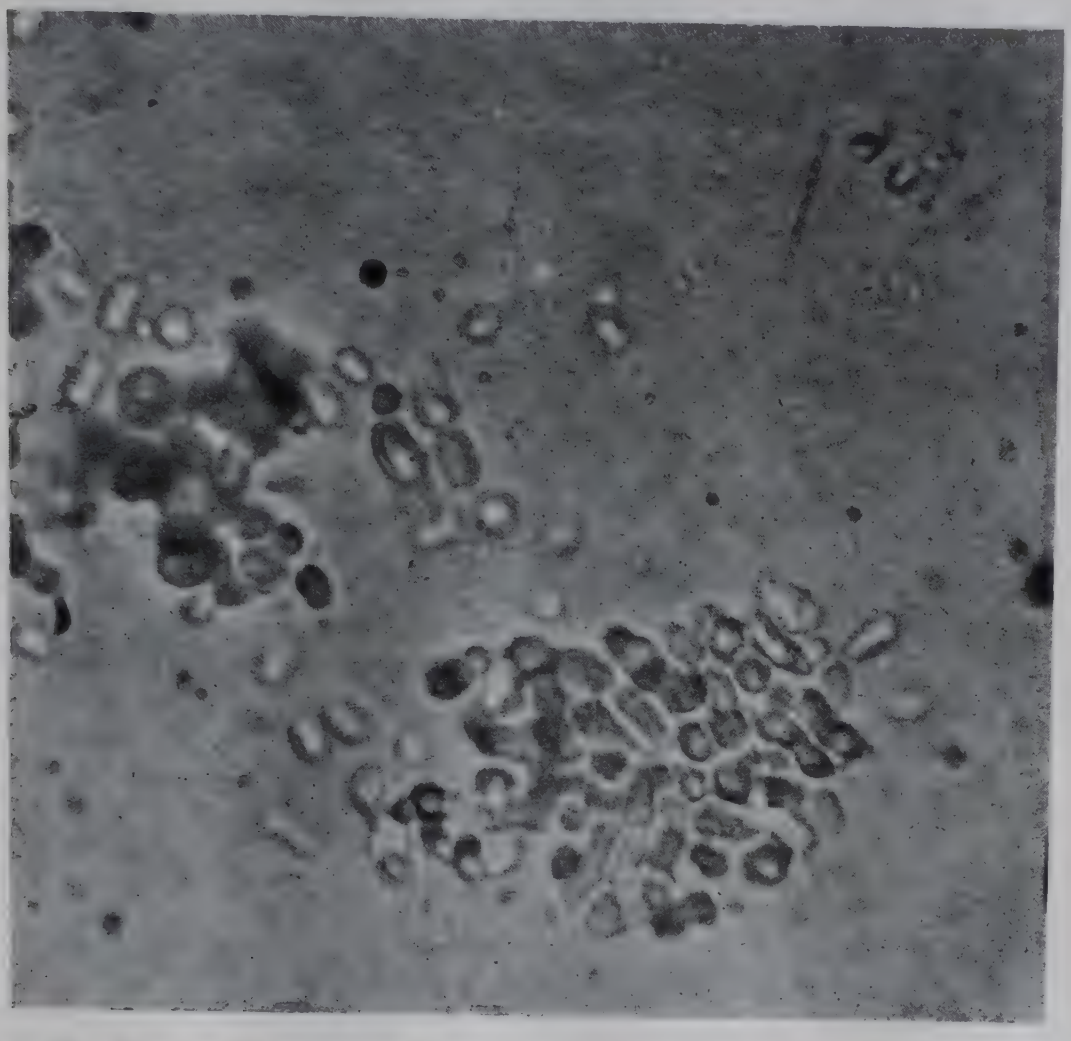

FIG. 63. SPORES VARYING IN SIZE AND SHAPE (SOME SAUSAGE-SHAPED) IN CRUSTS (SCUTULA) OF TINEA FAVOSA. × 600

characteristic growth. When full-grown, the colony is compact, smooth, and waxy; it is usually described as of "basket type," varying from white to brown in color. Pleomorphism is uncommon.

Study of the hanging-drop preparation shows: (1) conidia-bearing hyphae, with lateral and apical spores, found on barley

and carrot media; on the other media, only arthrospores are present; (2) claviform bodies, with the terminal portions of some filaments swollen and claviform; some authorities compare these to the spindles of the Trichophyton and Microsporum

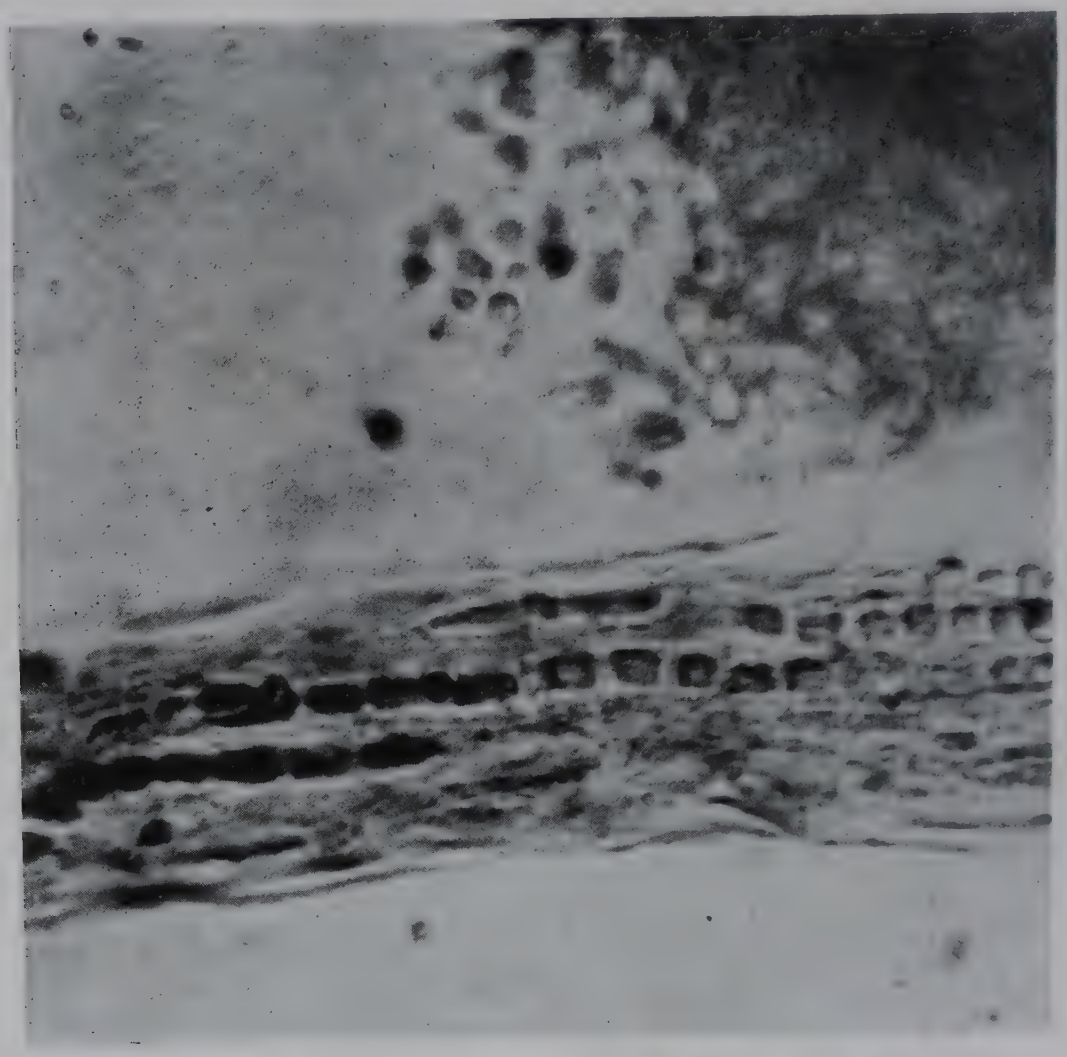

FIG. 64. SPORES AND MYCELIUM IN POTASSIUM HYDROXIDE PREPARATION OF HAIR IN TINEA FAVOSA. × 600

genera, though they are more slender and nonseptate—the French call them *chandeliers faviques*, because of their candlestick conformation; (3) terminal chlamydospores, varying in number.

Cutaneous sensitivity with resulting "id" reaction is rare. A reaction to an intracutaneous test with trichophytin is usually absent. Occasionally a mild response may be elicited.

Trichophyton Concentricum (Blanchard, 1896)

Synonyms: Endodermophyton concentricum; Endodermophyton indicum; Endodermophyton tropicale; Endodermophyton mansoni

This organism is the chief cause of tinea imbricata. The disease is common where the cocoanut tree grows, such as the

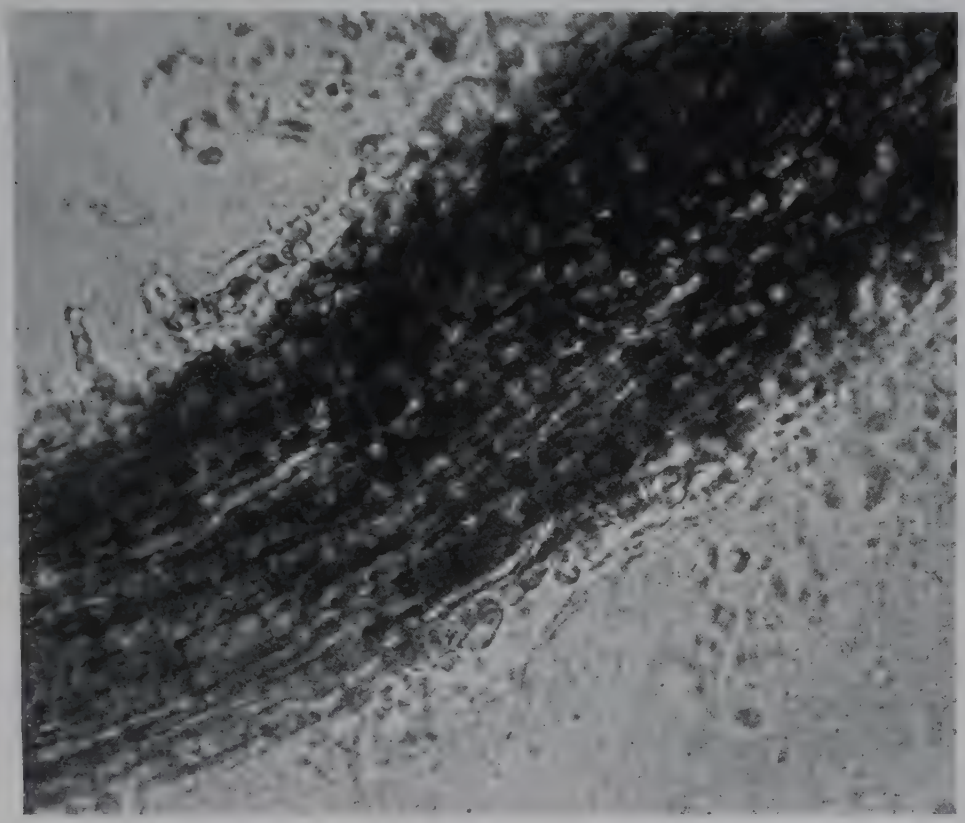

Fig. 65. Spores and Mycelium in Potassium Hydroxide Preparation of Hair in Tinea Favosa. × 500

Pacific Islands, the Malay States, and central and southern China. Young adults are more prone to contract the disease, and males are more susceptible than females.

MYCOLOGY

On direct microscopic examination of skin scales one finds numerous interlacing segmented hyphae. For cultural studies, the scales should first be soaked in alcohol for five minutes to

avoid contamination with bacteria. These scales are then placed in Sabouraud's broth. After several weeks the fluffy growth is transferred to Sabouraud's dextrose agar. The growth on the solid medium is heaped, deeply folded, glabrous and white at first. It soon becomes deep brown in the center

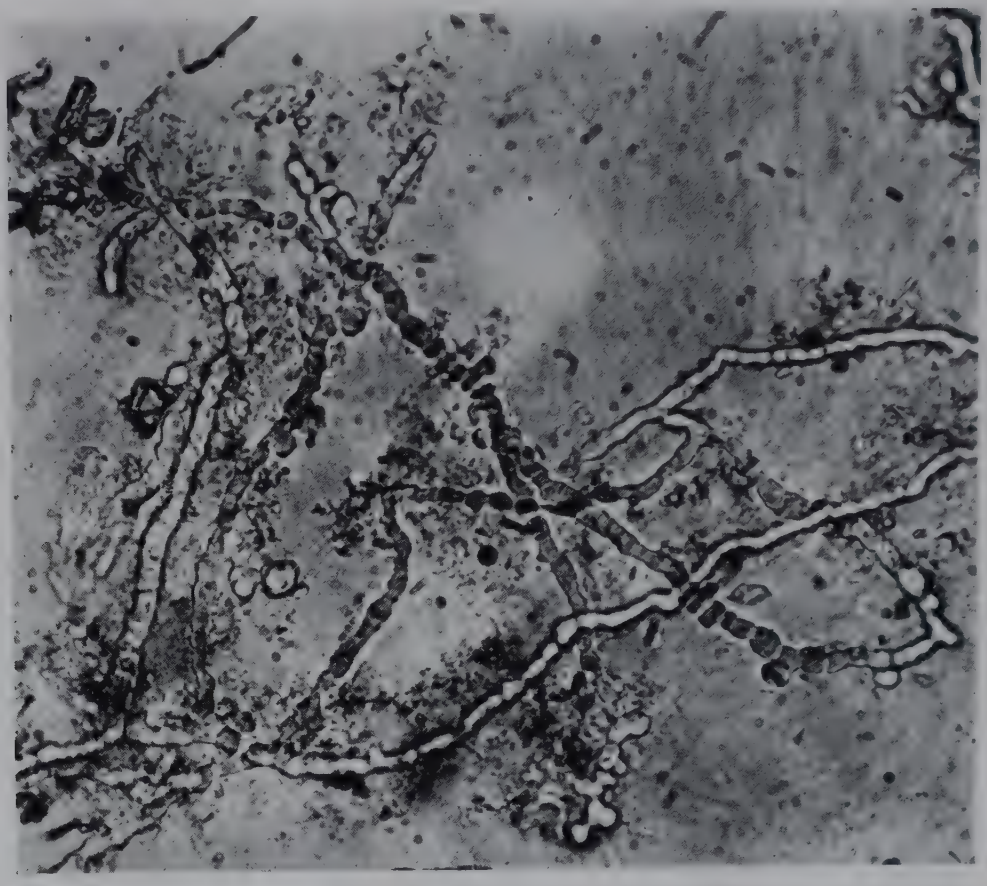

FIG. 66. POTASSIUM HYDROXIDE PREPARATION OF SCRAPINGS FROM NAIL INFECTED WITH T. SCHOENLEINI. × 550

with a cream-colored and powdery periphery. The substrate is pigmented deep amber in color. The resemblance to T. schoenleini is striking. On culture mount one sees numerous vegetative forms and arthrospores but no microconidia.

GENUS EPIDERMOPHYTON

Species: Epidermophyton inguinale (Sabouraud, 1910); Epidermophyton floccosum (Langeron and Milochevitch, 1930)

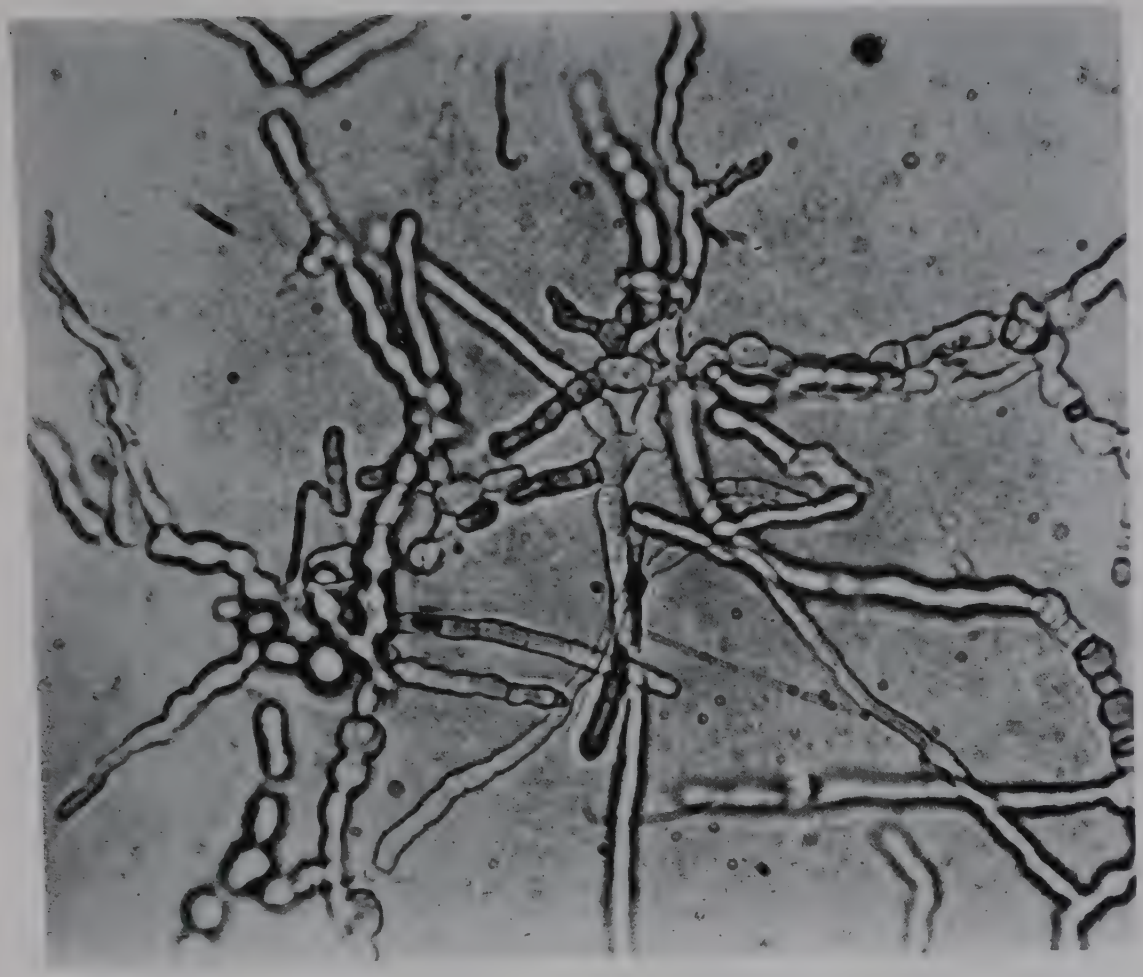

FIG. 67. TRICHOPHYTON (ACHORION) SCHOENLEINI.

Hanging-drop preparation showing *chandelier favique* and chlamydospores. × 900

This organism produces the clinical entities tinea cruris and dermatophytosis of the hands and feet. Only glabrous skin and the nails are susceptible, the parasite showing an affinity for the skin of the inguinal fold, intergluteal fold, axillae, feet, and hands. Hair is never affected.

MYCOLOGY

The colony is slow-growing and greenish yellow in color showing radial furrows. Pleomorphism occurs. Microscopic examination shows septate mycelium with terminal clavate-

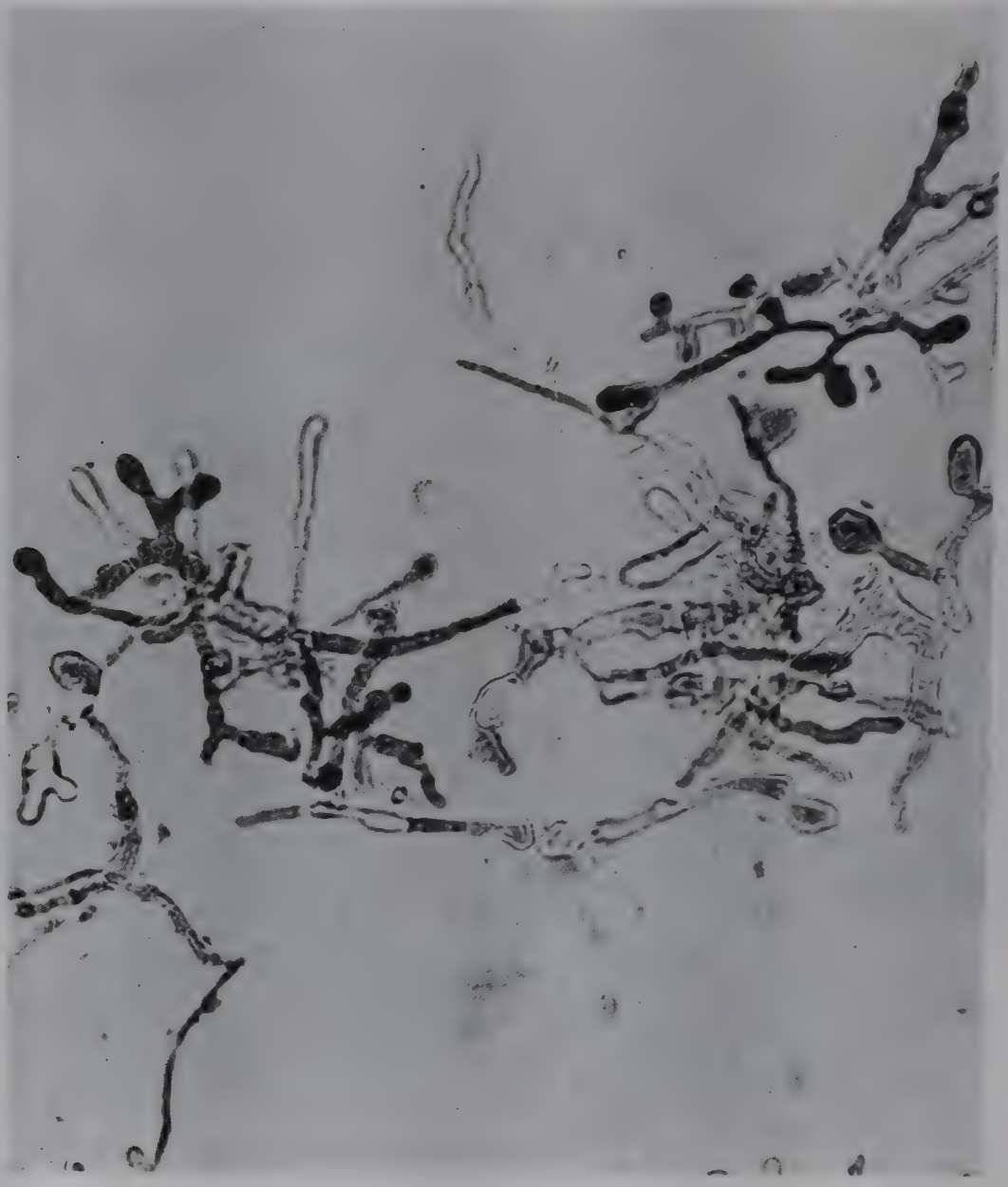

FIG. 68. TRICHOPHYTON (ACHORION) SCHOENLEINI
Culture mount (stained) showing *chandelier favique* and chlamydospores. × 600

shaped fuseaux, which may appear singly or in groups of five to seven, and chlamydospores, these occasionally in abundance. Aleurospores are very rare.

Cutaneous sensitivity with resulting "id" reaction is not common. An intracutaneous test with trichophytin usually elicits a negative or a mildly positive reaction.

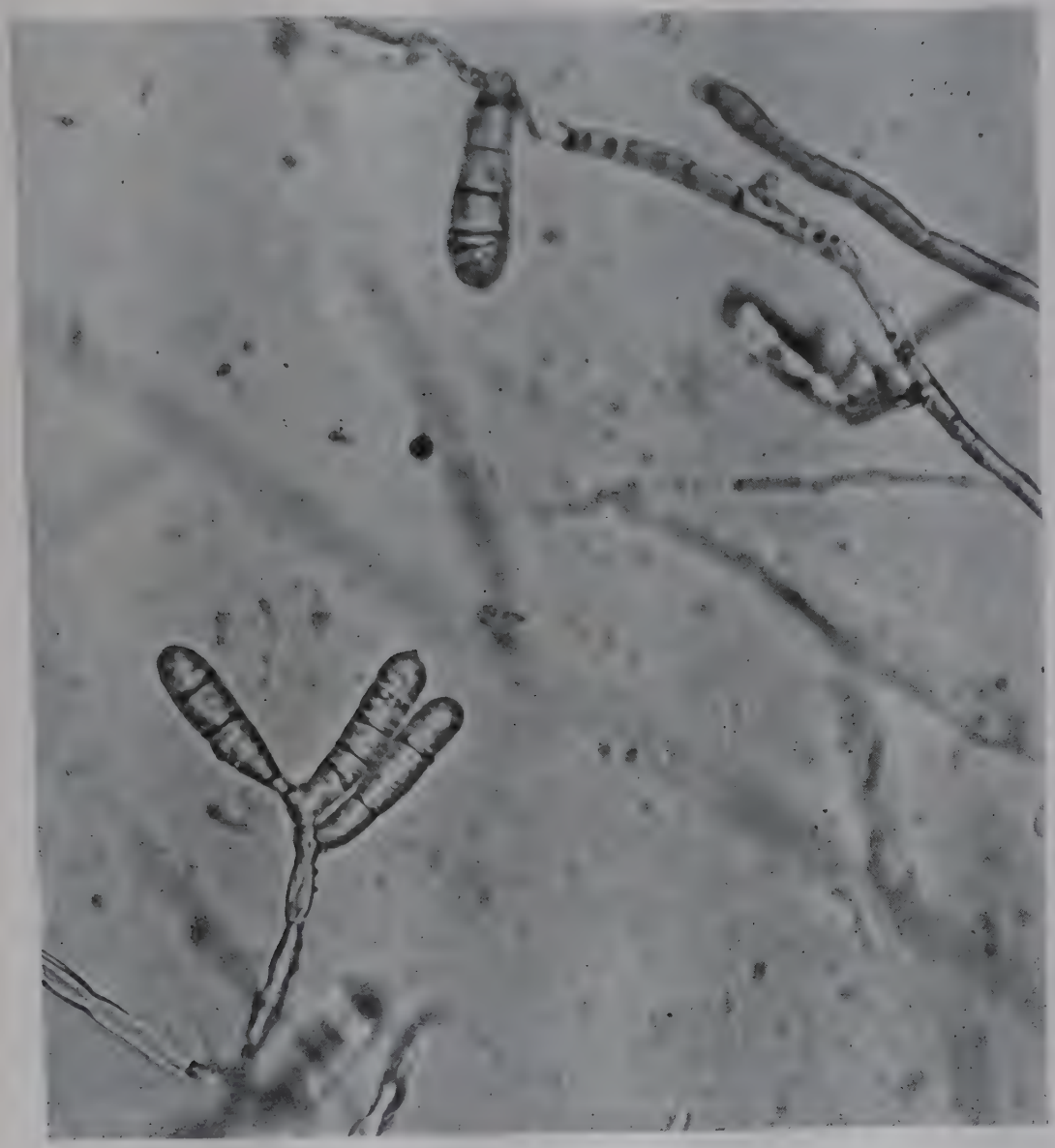

FIG. 69. GENUS EPIDERMOPHYTON
Culture mount showing finger-like projection of club-shaped fuseaux (macroconidia) and absence of conidia. × 700

CLINICAL CONSIDERATIONS

Tinea capitis and *tinea circinata* have already been described clinically (see pp. 72–85).

TINEA FAVOSA

Clinical Picture. This condition affects chiefly the scalp, but can affect glabrous skin and the nails. It is caused by the

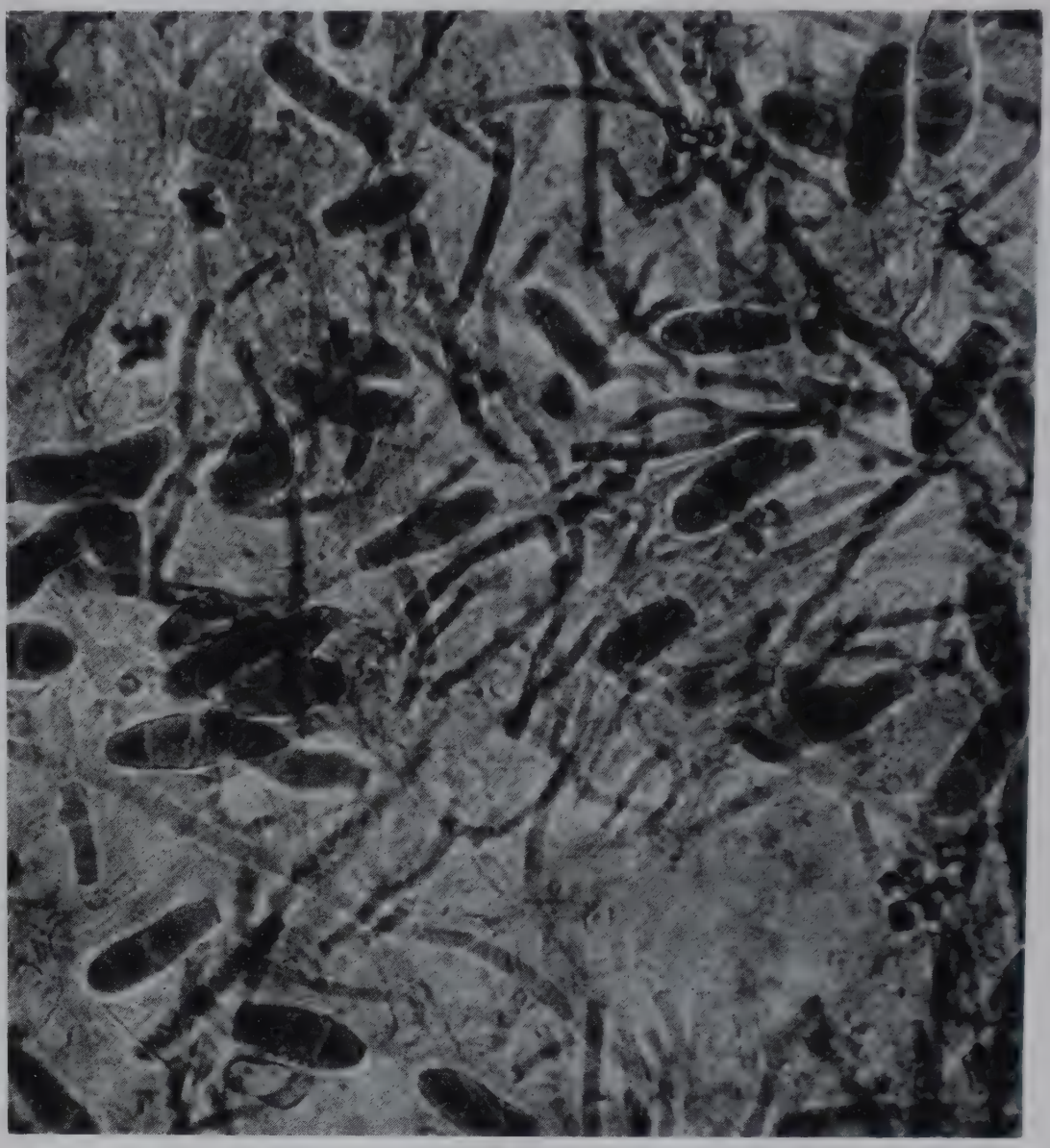

FIG. 70. NUMEROUS CLUB-SHAPED FUSEAUX (MACROCONIDIA) IN GENUS EPIDERMOPHYTON. × 700

micro-organism known as Trichophyton (Achorion) schoenleini. No age or sex is immune. On the scalp the disease usually starts as a small inflammatory area covered with scales. Yellowish (sulfur-colored) crusts form around the hair follicle. The crusts increase in size and finally become hollow cup-shaped, pierced by hairs. These crusts are known as scutula and are particularly found at the border of the involved areas. Brittleness and loss of hair are typical. Atrophic scarring occurs

FIG. 71. E. FLOCCOSUM

Culture mount showing chlamydospores and mycelium; conspicuous absence of microconidia. × 500

and in long-standing cases the odor is extremely offensive, frequently referred to as a mousy odor.

Favus of the scalp in adults may also resemble seborrhoic dermatitis showing diffuse superficial adherent scaling with little scarring and follicular involvement. Its resistance to the usual therapy for seborrhea of the scalp should make one suspect favus. Favus of glabrous skin appears as numerous or few and scattered crusts that are yellowish and cup-shaped, with no noticeable inflammation. In the nails the organism pro-

FIG. 72. TINEA FAVOSA SHOWING SCARRING AND SCUTULA

duces a yellowish discoloration, evidence of destruction, and brittleness. Primary favus of the nails in this country has been reported by one of the authors (J. H. S.) and also by Lewis.

A reaction to an intracutaneous test with trichophytin is usually absent.

Animals are the most common means of transmission, especially cats. Other modes are direct contact with infected humans, contaminated clothing, and the comb and brush.

FIG. 73. FAVUS OF SCALP

Treatment. Since the disease is inoculable, the source of infection must be found and eliminated. The most effective therapeutic measure is roentgen ray epilation (see Treatment of Tinea Capitis); even this sometimes fails, however. Ethyl iodide inhalation is employed as in tinea capitis. In most cases, a combination of roentgen ray epilation and ethyl iodide inhalation is advisable.

TINEA SYCOSIS (TINEA BARBAE)

Clinical Picture. The causative micro-organisms are T. gypseum, T. rosaceum, T. violaceum, and M. canis. T. gypseum is the cause of the majority of cases of tinea barbae. This disease invades the bearded region, with the exception of the

upper lip, which is only rarely involved. The lesions take the form of minute to large abscesses of follicular distribution, exuding a gelatinous fluid. In this fluid or in the hairs will be found mycelium and spores, verifying the diagnosis and helping

FIG. 74. FAVUS OF THE SCALP AND GLABROUS SKIN

to differentiate the disorder from sycosis vulgaris. The clinical picture may vary from a type simulating sycosis vulgaris to the extreme kerion type. The latter is more common when the causative agent is either T. gypseum or M. canis.

FIG. 75. FAVUS OF THE SCALP (Burned out)

Treatment. Two phases are important. They consist of:

1. Precautionary measures in shaving. The patient is instructed (*a*) to use no brush, because it cannot be sterilized; (*b*) to shave the healthy skin first and the involved skin last; (*c*) to avoid traumatizing the skin.

FIG. 76. FAVUS OF THE NAILS IN PATIENT WITH FAVUS OF THE SCALP (FIG. 75)

2. Manual epilation of the involved hairs and daily or twice-daily application of the following ointment:

		Gm. or cc.
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0
ℿ		

In some extremely stubborn and extensive cases, roentgen ray epilation may be necessary, and ethyl iodide inhalation can also be tried.

ONYCHOMYCOSIS

Clinical Picture. One or more of the nails may be invaded, giving a brittle, yellowish brown or darker, and lusterless, pitted appearance. The parts chiefly affected are the nail bed and the lateral aspects. Beneath these affected parts, particularly the lateral margins, are accumulations of soft debris. An accompanying inflammation about the nail is rare (paronychia). The course is chronic.

Treatment. Results are not very satisfactory. The following measures are employed for local treatment:

1. Soak the fingernails for fifteen minutes in a warm saturated solution of boric acid (1 teaspoonful of boric acid crystals to a glass of warm water).
2. Scrape the affected nail until it hurts, using either the rough side of a broken glass slide or a sharp scalpel. The use of a burr powered by a small motor to remove the infected nail material is advisable only in selected cases.
3. Apply morning and night, after soaking, one of the following ointments to the nail and beneath it.

	Gm. or cc.
℞ Acidi salicylici	2.0
Acidi benzoici	2.0
Petrolati	30.0

℥

	Gm. or cc.
℞ Mercurochrome crystals	0.6
Aquae	1.2
Acidi salicylici	2.0
Petrolati	
Lanolini aa, ad	30.0

℥

	Gm. or cc.
Sodium propionate	9.84
Propionic acid	2.16
N-propyl alcohol	6.0
Zinc carbonate	3.0
Carbowax 4000	39.0

A sodium perborate paste made up of a few drops of water added to sodium perborate powder is applied to the fingernail and nail bed and covered with a rubber finger cot, and allowed to remain overnight.

In roentgen ray therapy, each nail is treated separately, the skin being protected with a lead filter.

FIG. 77. ONYCHOMYCOSIS (T. RUBRUM)

Surgery, followed by local treatment, is also employed but only as a last resort. The nail is removed surgically and the nail bed is soaked in boric acid solution as described above; this is followed by application of the mercurochrome ointment.

Ethyl iodide inhalations are rather disappointing in onychomycosis.

DERMATOPHYTOSIS

Also known as epidermomycosis, dermatomycosis, and eczema mycoticum, this term usually refers to a superficial fungus infection of intertrigenous or other areas of the glabrous skin. Under this heading are included tinea pedis, tinea manuum, allergic manifestations (dermatophytids), and tinea

cruris. Onychomycosis is discussed separately (see p. 120). Tinea pedis or tinea manuum may be accompanied by nail involvement. The inflammatory and acute type of this disease is more frequently caused by T. gypseum, whereas the chronic type is more frequently seen when T. rubrum (purpureum) is the causative agent.

FIG. 78. ONYCHOMYCOSIS (T. GYPSEUM)

Tinea pedis and tinea manuum are rare in children under the age of puberty and such a diagnosis in children should be made only when supported by direct microscopic examination and cultural studies. Tinea manuum is not a common occurrence in children or adults. Not every vesicular or scaly eruption on the hands is due to a fungus infection. When a diagnosis of tinea manuum is made, the burden of proof is on

the one who makes the diagnosis and should therefore be supported by positive mycologic studies.

This clinical entity may take any one of several distinct forms or represent a combination of all of them, with one form predominating. The eruption is erythematous, papular, scaly, vesicular, macerated, fissured, or hyperkeratotic.

Erythematous Form. This form usually consists of a patch of erythema, often sharply demarcated, especially at the lower

FIG. 79. DERMATOPHYTOSIS OF FOOT (INTERTRIGENOUS TYPE)

border, with slight elevation and minute vesiculation. Clearing in the center may take place. In brunettes or in persons with a tendency to pigment, superpigmentation in varying degrees may be noted. Lichenification is present in long-standing cases. In folds, there are also maceration, fissuring, papulation, and pustulation. The seat of predilection of this type of lesion is the upper inner aspect of the thigh, with extension to the groin and posteriorly to the intergluteal fold.

FIG. 80. DERMATOPHYTOSIS OF FOOT (SCALY TYPE)

At times the genitalia are involved. The progress of the eruption may be upward and may involve the pubis, but never the pubic hair. The thighs and their environs are not the only seat of this form of dermatophytosis. The axillae are not infrequently infected. The area under the breasts, especially when they are pendulous, may become involved, and, in addition to erythema and fine scaling, there may be papulation and pustulation.

Papular Form. This type of the disease is rather less common. It may occur on the free surfaces or where cutaneous areas oppose each other. In the former case the eruption is

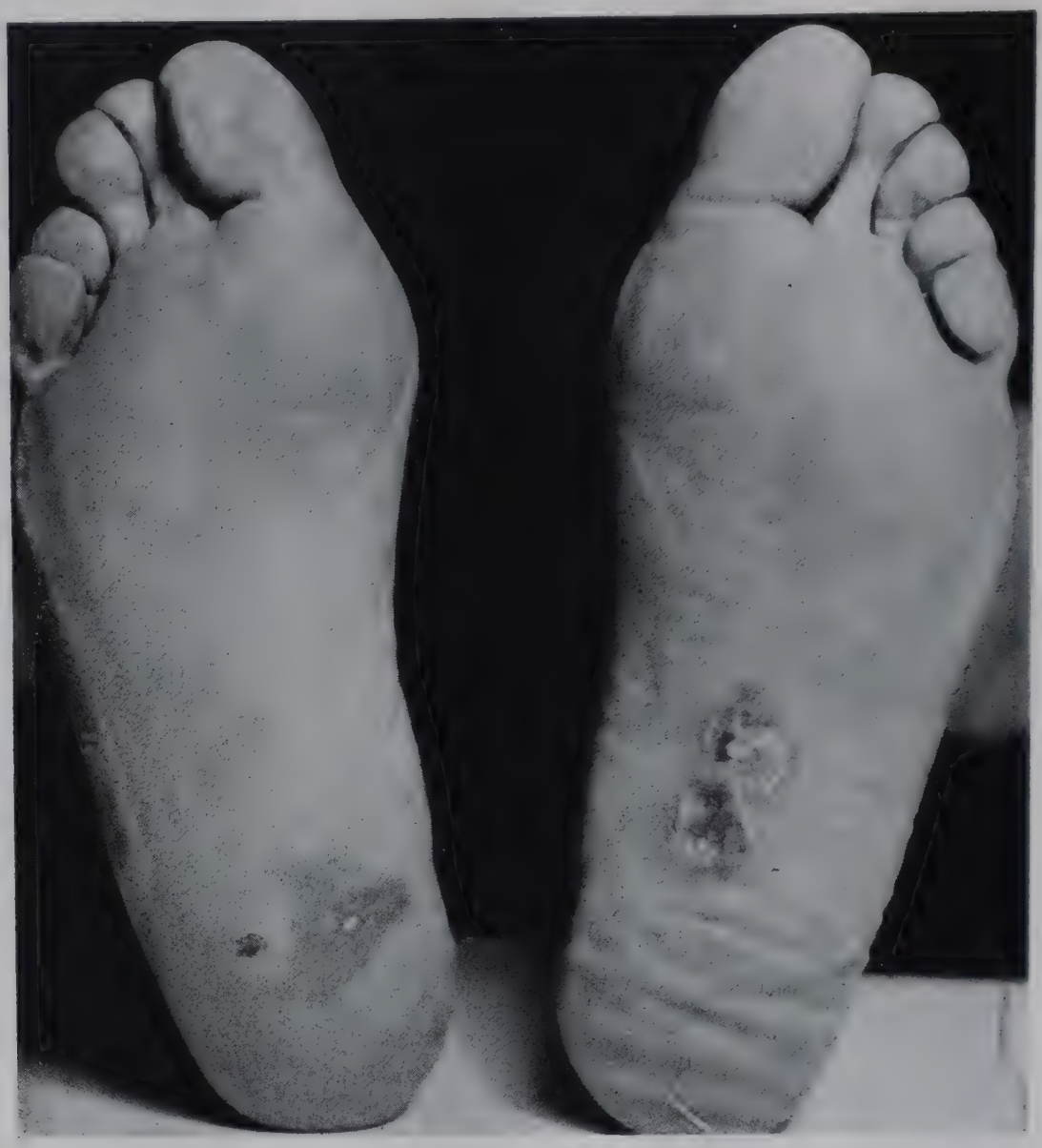

FIG. 81. DERMATOPHYTOSIS OF FOOT (VESICULAR TYPE)

dry, whereas in the latter the lesions become red, moist, erosive, and show superimposed pustulation.

Scaly Form. Scaling in dermatophytosis may be a primary process or may be secondary to any other form of the disease. In the primary type, scales are most commonly observed on the sides of the fingers or on the toes, in their webs, on the palms, or on the soles. The scales may be few, or they may be so pronounced or so numerous that the patient himself cannot fail to observe them. The fourth interspace is the favorite seat of

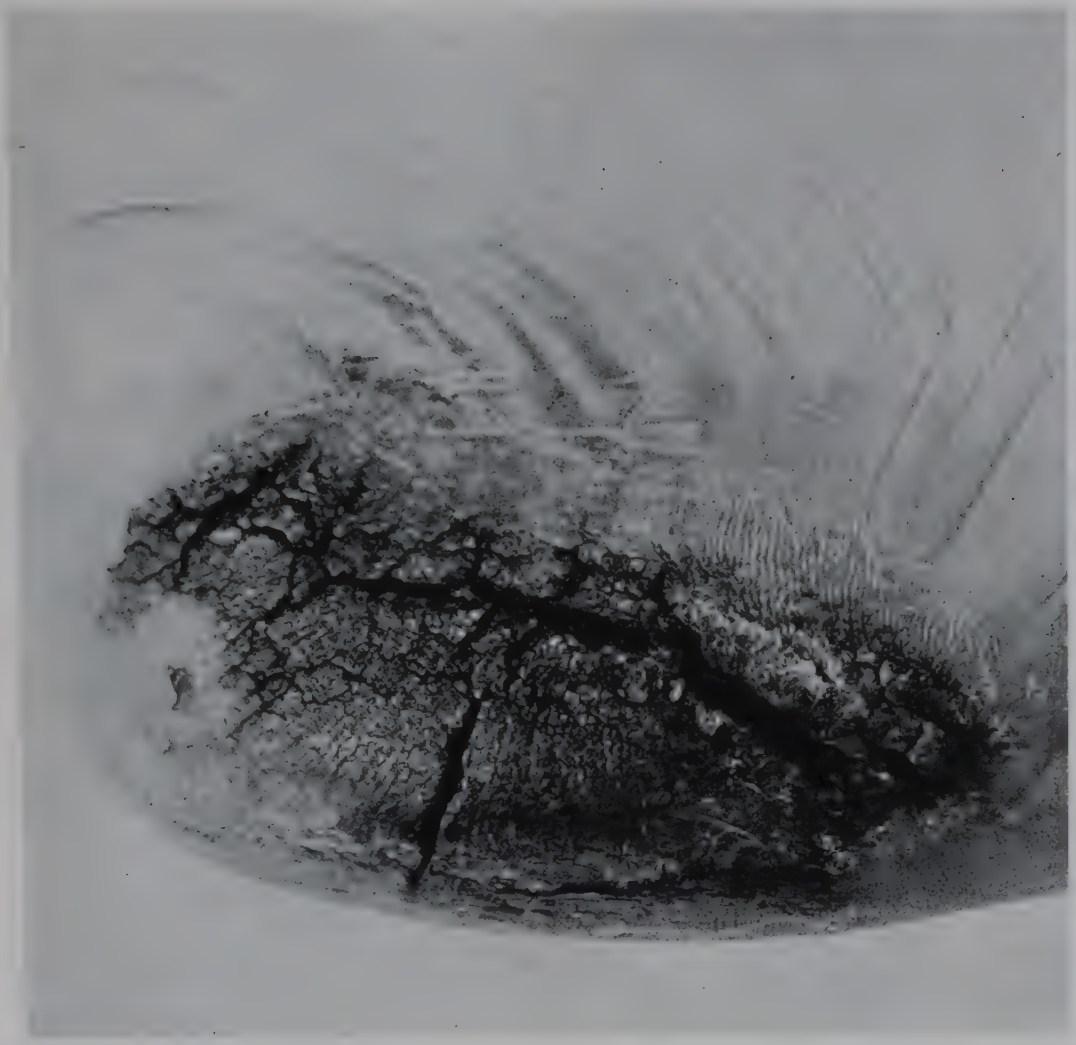

FIG. 82. DERMATOPHYTOSIS OF FOOT (HYPERKERATOTIC TYPE)

the scales, followed by the third interspace as a poor second. The fourth interspace of the left foot is usually more frequently and more noticeably involved.

Vesicular Form. This is the most common form of the disease. It is seen as primary lesions on the palms, the lateral and palmar aspects of fingers, the soles of the feet, and the toes. The vesicles are usually intradermal. They tend to be discrete but may coalesce. The vesicles often have a dark steel blue center and turn brown with age. Bullae may be present. On the soles of the feet the vesicles are most frequently seen on the arch.

Macerated Form. The seats of predilection of this form are the webs of the toes, the intergluteal fold, the contact points of the penis and scrotum, the submammary folds, and the axillary folds. The fourth toe space, particularly that of the left foot, is the most common site. Inflammation may or may not accompany this form; it is most frequently seen in the intergluteal and submammary folds.

FIG. 83. DERMATOPHYTOSIS OF HAND

Fissured Form. This form is relatively more frequently seen between toes. It may be found accompanying the hyperkeratotic type of epidermophytosis on the soles of the feet. Fissuring in the intergluteal and submammary folds is usually not primary, but accompanies the macerated or erythematous form.

Hyperkeratotic Form. This is particularly seen on the soles of the feet and occasionally on the palms. The lesions ap-

FIG. 84. DERMATOPHYTOSIS OF HAND (HYPERKERATOTIC TYPE)
Patient had nail involvement (Fig. 78)

pear as orange-colored hyperkeratotic areas accompanied by fissuring, sometimes quite deep and painful.

A concomitant toxic or allergic eruption, known widely as *trichophytid,* may also be present. It is symmetric and appears commonly on the extremities, particularly the upper ones. It may be macular, papular, or vesicular in character or follicular, lichenified, or squamous. The organism cannot be seen microscopically in these lesions.

The form of infection that involves the upper regions of the thighs, and sometimes extends to the perineum and beyond to

the intergluteal fold, is frequently called eczema marginatum, *tinea cruris*, or dhobie itch. The characteristic lesion is a patch of erythema often sharply demarcated and showing maceration in the fold and a slightly elevated border frequently consisting of pin-point vesicles. It tends to clear centrally while extending peripherally. In brunettes or persons with a tendency to pigment, superpigmentation in varying degrees

FIG. 85. TRICHOPHYTON RUBRUM (PURPUREUM) INFECTION

may be noted. Lichenification is present in long-standing cases. Because of the heat and moisture in the intergluteal fold, the predominating characteristics may be maceration and fissuring.

Lymphangitis and regional lymphadenitis may complicate dermatophytosis, particularly when the lower extremities are involved. These are usually due to a superimposed bacterial infection but may be due directly to the fungus infection.

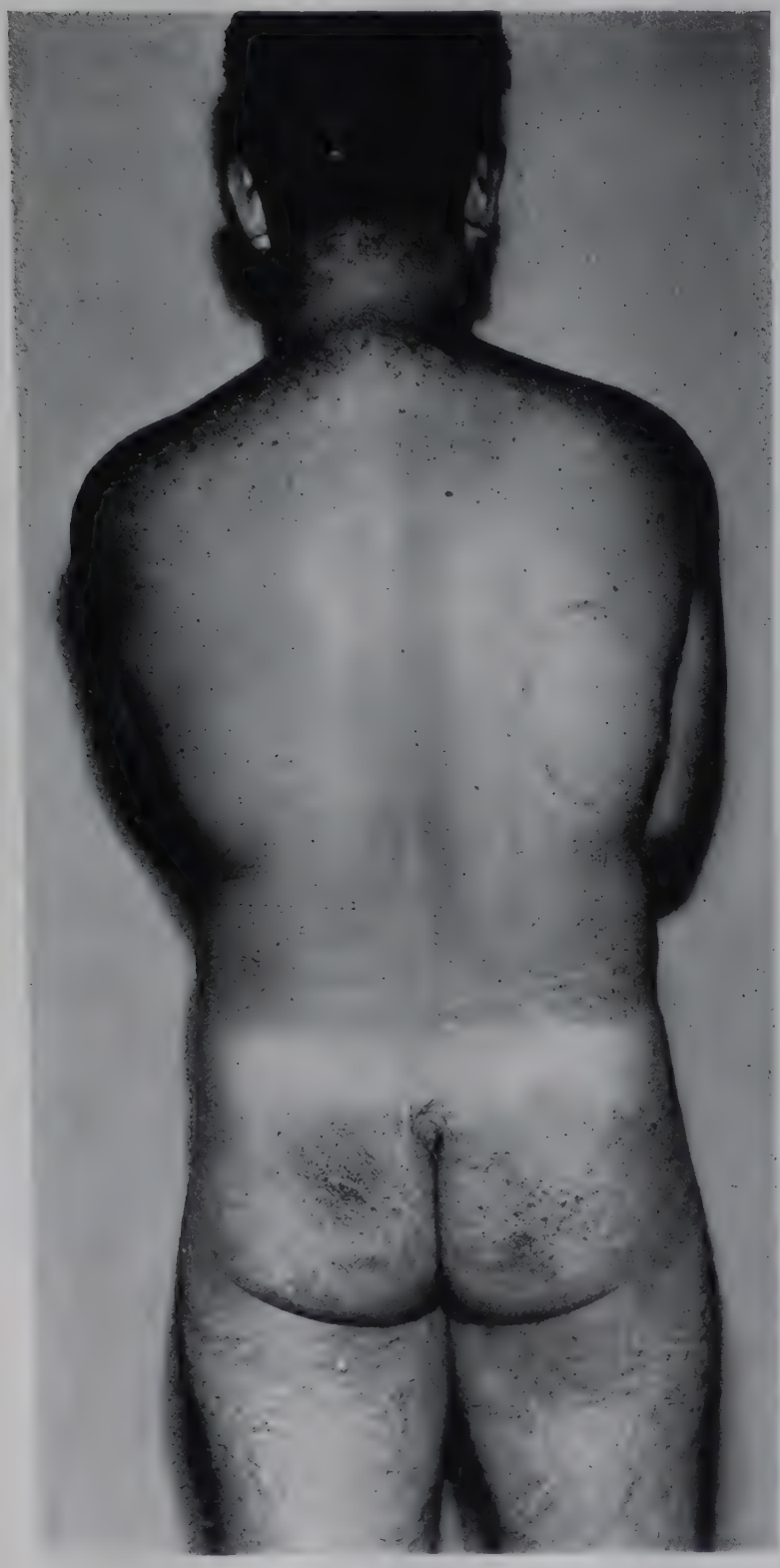

FIG. 86. TRICHOPHYTON RUBRUM (PURPUREUM) INFECTION

FIG. 87. TRICHOPHYTON RUBRUM (PURPUREUM) INFECTION IN PATIENT SHOWN IN FIG. 86

Dermatophytosis caused by T. rubrum or T. purpureum appears as an extensive, rather stubborn infection of glabrous skin and nails, clinically resembling the ordinary dermatophytosis produced by T. gypseum, or taking the form of a bizarre pattern of lesions involving the trunk and extremities. This infection is notable for its chronic character. Trichophyton rubrum practically never produces vesiculation or acute reaction. Hopkins and his group, however, reported vesicular lesions in many of the patients with T. rubrum infections studied at Fort Benning, 1942–45. This may be explained by a difference in strain of T. rubrum, climate, and possibly by increased sensitivity of the host.

The absence of vesiculation, acute reaction, and the presence of chronicity should suggest T. rubrum as the causative agent of tinea pedis and tinea manuum but in the final analysis, cultural study is the most accurate means of determining the causative micro-organism. The condition has been described in detail by Lewis, Montgomery, and Hopper, and by the author (J. H. S.) and Conant.

FIG. 88. VESICULAR DERMATOPHYTID

Tricophytid, Epidermophytid, Dermatophytid. The so-called "id" eruptions are manifestations of cutaneous allergy due to a hematogenous extension from an active focus of fungus infection. The lesions in themselves are sterile—that is, the presence of fungi cannot be demonstrated either by direct microscopic examination or by culture. The eruption varies from an

eczematous, vesicular, or erythematous type to one simulating erythema multiforme. The extremities are the most common site. The term dermatophytid has been considerably abused particularly in the United States. Erythematous, vesicular, and eczematous eruptions on the hand have been carelessly labelled dermatophytid without any proof of a focus of infec-

FIG. 89. TINEA CRURIS (E. FLOCCOSUM)

tion. For a definite diagnosis of dermatophytid, an active focus must be present. A positive trichophytin test is helpful. The eruption should clear with the subsidence of the active focal infection except when there are secondary eczematous changes due to sensitivity to other substances or to overtreatment.

Treatment. There is no specific treatment in dermatophytosis. An accurate diagnosis is essential for proper treatment. A clinical diagnosis should always be confirmed by direct microscopic examinations and cultural studies. The latter will assist in determining the prognosis and the type of therapy, since treatment is based upon the type of fungus isolated, cutaneous sensitization or the lack of it, and the clinical findings. If T. gypseum is cultured from the lesions, therapy is usually effective. On the other hand, if T. rubrum is the offending agent, response to therapy is not too good. In the *acute stage* one cannot stress too much the importance of gentle, nonirritating treatment. Warm boric soaks or potassium permanganate (1:5,000) soaks should be used for ten to fifteen minutes two or three times a day, followed by the use of a soothing antipruritic lotion:

		Gm. or cc.
℞	Mentholis	0.3
	Zinci oxidi	8.0
	Calamini	4.0
	Phenolis	2.0
	Liquor calcis ad	240.0

℥

When desquammation or crusting takes place, this treatment is continued, with the addition of the following ointment:

		Gm. or cc.
℞	Acidi borici	2.0
	Zinci oxidi	2.0
	Amyli	8.0
	Petrolati	30.0

℥

Rest and elevation of the extremities are essential. The patient is not to use stimulating or irritating preparations.

In the *chronic stage*, effective local treatment may be given in the form of fungicidal preparations: iodine, thymol, oil of cinnamon, chrysarobin, potassium permanganate, copper sulfate, gentian violet, mercurochrome, sodium hyposulfite,

sulfur, benzoic acid, and salicylic acid. A keratolytic agent and a soft penetrating base are necessary in most cases.

The following are some of the ointments in use:

		Gm. or cc.
℞	Iodine crystals	0.3–0.6
	Potassium iodide (enough to dissolve iodine)	
	Acidi salicylici	2.0
	Lanolini —	
	Petrolati aa ad	30.0
ℿ		
℞	Mercurochrome crystals	0.6–1.2
	Aquae	1.2–1.8
	Acidi salicylici	2.0
	Lanolini	
	Petrolati aa ad	30.0
ℿ		
	(Useful in vesicular and pustular types)	
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0
ℿ		
℞	Acidi salicylici	2.0
	Acidi benzoici	4.0
	Adipis	30.0
ℿ		
	(Whitfield's ointment)	
		Gm. or cc.
℞	Acidi salicylici	1.0
	Acidi benzoici	1.5
	Paraffini mollis	8.0
	Olei cocois nuciferae	30.0
ℿ		
	(Modified Whitfield's ointment)	
℞	Thymolis	0.3
	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0
ℿ		

℞	Chrysarobini	1.0
	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0

℔

(Useful for the hyperkeratotic type)

	Gm. or cc.
Sodium propionate*	12.3
Propionic acid	2.7
Sodium caprylate	10.0
Zinc caprylate	5.0
Dioctyl sodium sulfosuccinate	0.1
Carbowax 4000	69.9

℔

Hopkins and his co-workers found undecylenic acid (5 per cent) in carbowax to be effective.

Potassium permanganate in the strength of 0.05 to 1 per cent is used effectively in the vesicular stage, either alone or together with any of the above given ointments. In all instances, the application of the ointment should be preceded by soaking of the hands or feet in a warm saturated solution of boric acid.

After subsidence of the infection, the ointment is used at night only, instead of both morning and night. The soakings, however, are continued twice daily and, in the morning, can be followed by a light dusting with zinc oxide, boric acid, and talc in equal parts or with the following:

		Percentage
℞	Acidi salicylici	2.0
	Acidi benzoici	2.0
	Talci	96.0

℔

	Gm. or cc.
Calcium propionate*	15.0
Zinc propionate	5.0
Zinc caprylate	5.0
Base	75.0

* May be obtained from the Mycoloid Laboratories, Inc., Little Falls, New Jersey, as sopronol ointment and sopronol powder, respectively.

Instructions to be given the patient as to treatment are as follows:

Evening treatment

1. Soak the feet or hands for fifteen minutes in either a saturated solution of boric acid or 1:5,000 potassium permanganate.
2. Dry the affected parts with paper tissue or old towel. Do not use this towel on the rest of the body. Use a soft moist cotton ball to remove all loose skin.
3. Cover a toothpick with cotton and lightly brush the affected parts with ointment. Place a small piece of cotton cloth or bandage between the fingers or toes to prevent the skin areas from touching.
4. Protect bed linen by wearing old cotton stockings. The heel of a woman's stocking and the leg part are cut out, making two ties that can be fastened about the ankle to hold the dressing in position. On hands, wear cotton gloves from which the fingertips have been cut off.

Morning treatment

Wipe off all of the old ointment with a piece of tissue or cotton cloth. Powder the interdigital spaces and the insides of stockings and gloves.

If the feet only are affected, wash the hands carefully after treating the feet.

Care of wearing apparel

Proper equipment includes paper towels, 1 pint of formalin, a paper bag. Gather together all shoes and slippers worn during the infection. Soak paper towels in formalin and, carefully protecting the hands, stuff the soaked papers into the shoes and slippers. Place them in a large paper bag, tie this with string, and place it in a closet for twelve hours to fumigate. Remove the paper and place the shoes

and slippers in the sun for at least twenty-four hours to air before wearing them again.

Wear cotton stockings or gloves that can be boiled.

In acute vesicular infections, in those with accompanying epidermophytid or trichophytid, and in all stubborn, long-standing cases, ethyl iodide inhalation is effective and may be used. The inhaler of choice is one so designed as to allow a comfortable mixture of ethyl iodide and air. The initial dose is 1.5 cc. (3 Gm.); this is increased by 0.5 cc. (1 Gm.) per dose until 3 cc. is reached or, in the case of larger individuals, 4 cc. It usually requires about a half hour to inhale a dose of 3 cc. of the mixture. To avoid a cumulative effect, inhalations are given on two successive days, then omitted on the third. *Ethyl iodide should never be administered to patients suffering from pulmonary tuberculosis, toxic goiter, or nephritis.* The number of treatments varies with the site of the infection, its duration, and the nature of the invading organism. Yeast infections are relatively more resistant to treatment. For complications, see Treatment of Moniliasis (p. 56).

The use of ionization with copper sulfate described by Strauss and Haggard has been tried by the author in too few cases to provide sufficient basis for comment.

Tincture of metaphen has been found helpful in the interdigital and macerative types of infection.

In long-standing cases where lichenification and a good deal of pruritus are present, roentgen ray therapy, unfiltered, in doses of 50 to 75 r, has proved helpful. Roentgen rays are a poor fungicidal agent in doses that are harmless to the skin.

PROPHYLAXIS

Since mycotic organisms grow best in warm moist areas, preventive measures should be based on proper care of the body and on the elimination of every potential source of infection. The most common type of fungus infection seen by dermatologists is that which invades the feet. In an institution

such an infection becomes a serious problem. Prevention is possible if a few precautionary measures are observed and a general understanding of foot hygiene is maintained.

The chief rules of prophylaxis are:

1. Do not walk on floors in bare feet.
2. Do not wear any but your own slippers or shoes.
3. Place a towel on the floor of the shower or wear rubber bathing slippers.
4. Step from the tub or shower on to a fresh bath mat or newspapers.
5. Wash the feet at least once daily with soap and water.
6. Dry the feet thoroughly, leaving no moisture between the toes. Use a separate towel for the rest of body if any sign of infection, such as cracking, itching, or burning, is present. Powder the feet lightly, especially between the toes, using any borated (unscented) talcum. An excellent powder is a combination of equal parts of boric acid, zinc oxide, and talcum.
7. Boil all towels.

Care of the body

Persons who perspire freely are more susceptible than others to fungus infections. Daily baths and thorough drying of the body are essential. Application of an astringent lotion or powder to affected areas is helpful.

Care of the hands

Hands sensitive to soap and water, or hands that perspire easily, predispose to all types of skin infection. Care must be taken to observe the following precautionary measures:

1. Use a superfatted soap.
2. Dry the hands carefully. Never allow the hands to remain half damp. If there is a tendency to cracking, rub in toilet lanolin at least once daily.

3. If the hands perspire, soak them at least once a day in boric acid solution (1 teaspoonful to 1 pint of water). Never wear kid or tight gloves; wear cotton gloves and wash them after each wearing. Hydrosol solution (7 per cent), or a 10 per cent solution of aluminum chloride may be applied at night.

Rules applying to wearing apparel

1. Clothing: Clothing is a frequent source of reinfection. The underclothes should be of cotton and should be changed daily. Clothes should be washed with a bland, neutral soap and boiled, or pressed with a hot iron. Woolen sweaters or dresses should never be worn without some protection, such as dress shields or a lining. The necessity of cleansing such dresses and sweaters frequently, airing them weekly in the sun, and pressing them with a hot iron, cannot be overemphasized.
2. Stockings: Wear light cotton or silk stockings. Change at least once a day. Place soiled stockings in a separate laundry bag. When washing stockings, use mild, neutral soap. Whenever possible, dry them outdoors in the sun or press the feet of stockings with a hot iron before wearing. Never wear woolen stockings if the feet perspire.
3. Shoes: Two pairs of light-weight shoes are essential. Change shoes at least once a day. Never wear rubber-soled shoes or sneakers, as these make the feet perspire. Shoes with perforated tops are advisable in warm weather.

Care of bathroom and shower

These should preferably be in a sunny part of the house and the floors should be kept scrupulously clean and free of excess moisture. The floor of the shower should be such as not to allow water to collect and remain stagnant. The value of the antiseptic foot bath before and after tubbing has not been satisfactorily demonstrated.

Swimming pool precaution

The use of personal bathing shoes in going to and from a pool should be insisted upon.

TINEA IMBRICATA (TOKELAU)

This is a superficial fungus disease seen chiefly in the tropics or subtropics and caused by a micro-organism known as T. concentricum (E. concentricum). The infection begins as one or more brownish macules slowly increasing in size and forming concentric rings surrounded by a brownish zone. As a result of coalescence of adjacent concentric rings, polymorphic and polycyclic patches develop, which are characteristic for this disease. Scaling is usually profuse with little or no underlying erythema. Any part of the integument may become involved, including the nails. The hair follicles are usually spared. As a rule, itching is intense.

Treatment. The use of 5 or 10 per cent chrysarobin in aquaphor is recommended. Salicylic acid 6 per cent and sulfur precipitate 6 per cent in aquaphor, or Whitfield's ointment may be tried.

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CHAPTER VI

OTHER PATHOGENIC FUNGI

Blastomyces Dermatitidis

In a case diagnosed as scrofuloderma, Gilchrist in 1894 reported finding, in a section of diseased skin, a parasitic yeastlike body. Two years later, he published, with Stokes, the report of a second case in which this organism was discovered, and in 1898, in an extended study, named it Blastomyces dermatitidis. Since then, numerous reports on this fungus, by various authors, have appeared in the literature, most of them coming from the region around Chicago.

MYCOLOGY

A drop of either pus or sputum, with or without the addition of potassium hydroxide, is placed on a clean slide for direct microscopic examination. Budding thick-walled round or oval granular cells, from 8 to 10 microns or more in diameter, may be observed. If the suspected organism does not show budding, the cover glass used for the material not treated with potassium hydroxide may be rimmed with vaseline. After from twenty-four to forty-eight hours of incubation at room temperature, budding may be noted.

On culture (dextrose agar) at room temperature, the colonies first appear smooth and grayish, soon becoming filamentous and white, with a central umbo. A peripheral moist zone is usually present. On culture (blood agar) at 37 C., the surface growth is yeastlike, not filamentous.

Microscopic examination of a culture mount (dextrose agar) shows mycelium with lateral conidia and chlamydospores. Occasionally, racquet mycelium may be noted. On blood agar mounts, one sees budding cells similar to those seen in lesions, and occasional short filaments of three or four cells.

ANIMAL INOCULATION

The order of susceptibility is as follows: mice, rats, rabbits, guinea pigs.

IMMUNOLOGIC REACTION

Martin and Smith found that the majority of patients with blastomycosis react strongly to a heat-killed vaccine made from the yeastlike form of B. dermatitidis. Jacobson was unable to demonstrate specific reactions to vaccines. Cross sensitization with histoplasmin and occasionally with other antigens have been reported.

CLINICAL MANIFESTATIONS

The clinical picture is protean: it may simulate that of syphilis, tuberculosis, neoplasm, or disorders caused by other pathogenic fungi. The lesions may also resemble those of iodide or bromide sensitivity. The disease may take a cutaneous (primary and secondary) or systemic form.

Cutaneous Blastomycosis. In the *primary* form, the initial lesion is seen usually on the face, hands, wrists, and forearms, although it may appear anywhere on the skin. It is characteristically a papulopustule that soon becomes partially or wholly covered by a crust. Beneath the crust are irregular papilliform elevations and a seropurulent secretion. Peripheral growth of individual lesions and the appearance of new ones cause the formation of elevated various-sized plaques. Ormsby stresses the characteristic smooth purplish or dusky red border that slopes down abruptly to normal skin. In the border are superficial or deep minute abscesses that are visible only through a magnifying lens. These are the best material for recovery of the organism. Besides this type of lesion there are sometimes observed also a verrucous type simulating verrucous tuberculosis, and a deep-seated gummatous type. Spontaneous healing results in scarring.

The lesions of *secondary* cutaneous blastomycosis, the result

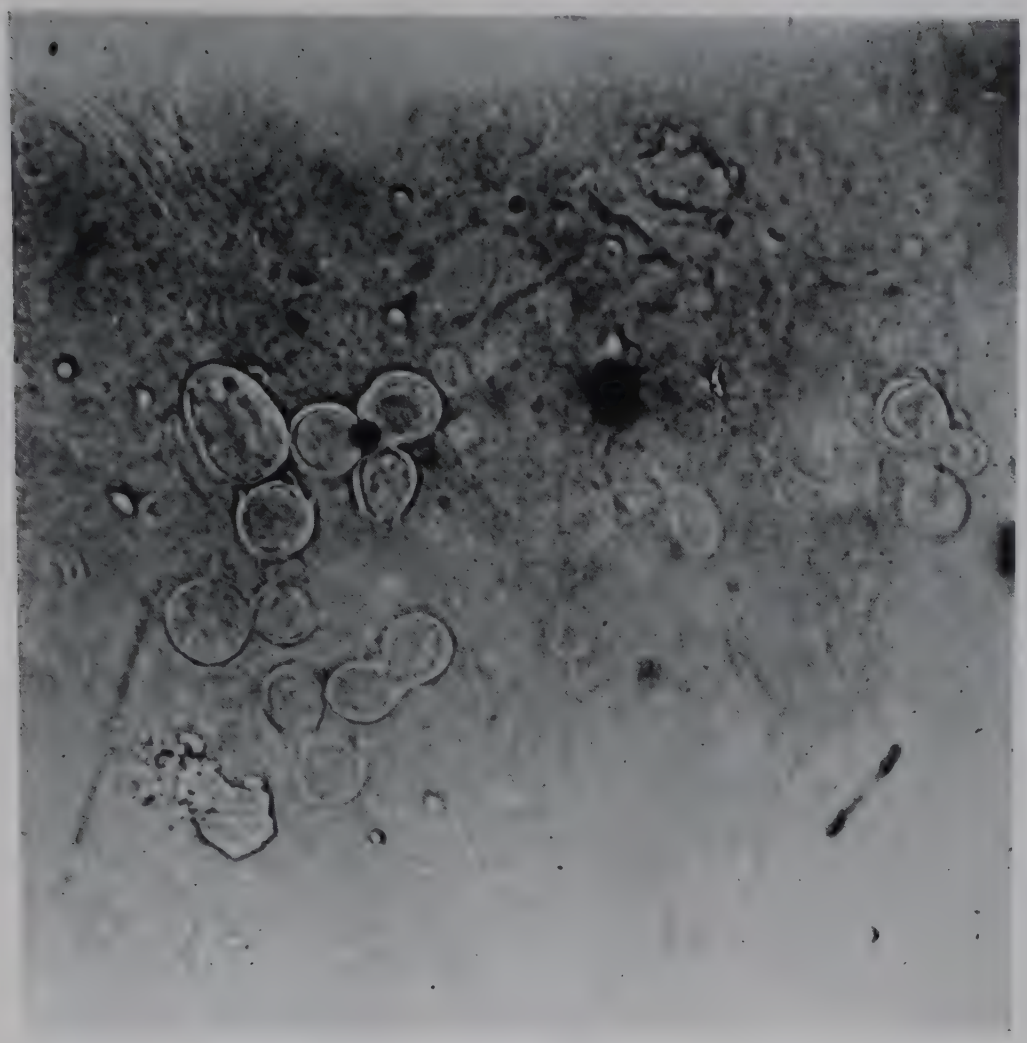

FIG. 90. BLASTOMYCOSIS ORGANISMS IN PUS
Potassium hydroxide preparation. × 950

of systemic blastomycosis, may simulate those of primary cutaneous blastomycosis or appear as ulcers usually having their origin in superficial or deep abscesses. The latter are usually associated with destructive processes in the bones, muscles, and other deep tissues and organs. Perinephric, psoas, abdominal, thoracic, and retropharyngeal abscesses of various size have been found.

Pulmonary Blastomycosis. The pulmonary involvement is more common'y primary but may be secondary to a focus in the skin. Systemic blastomycosis also shows an affinity for the lungs. The onset may be rapid and acute or marked by

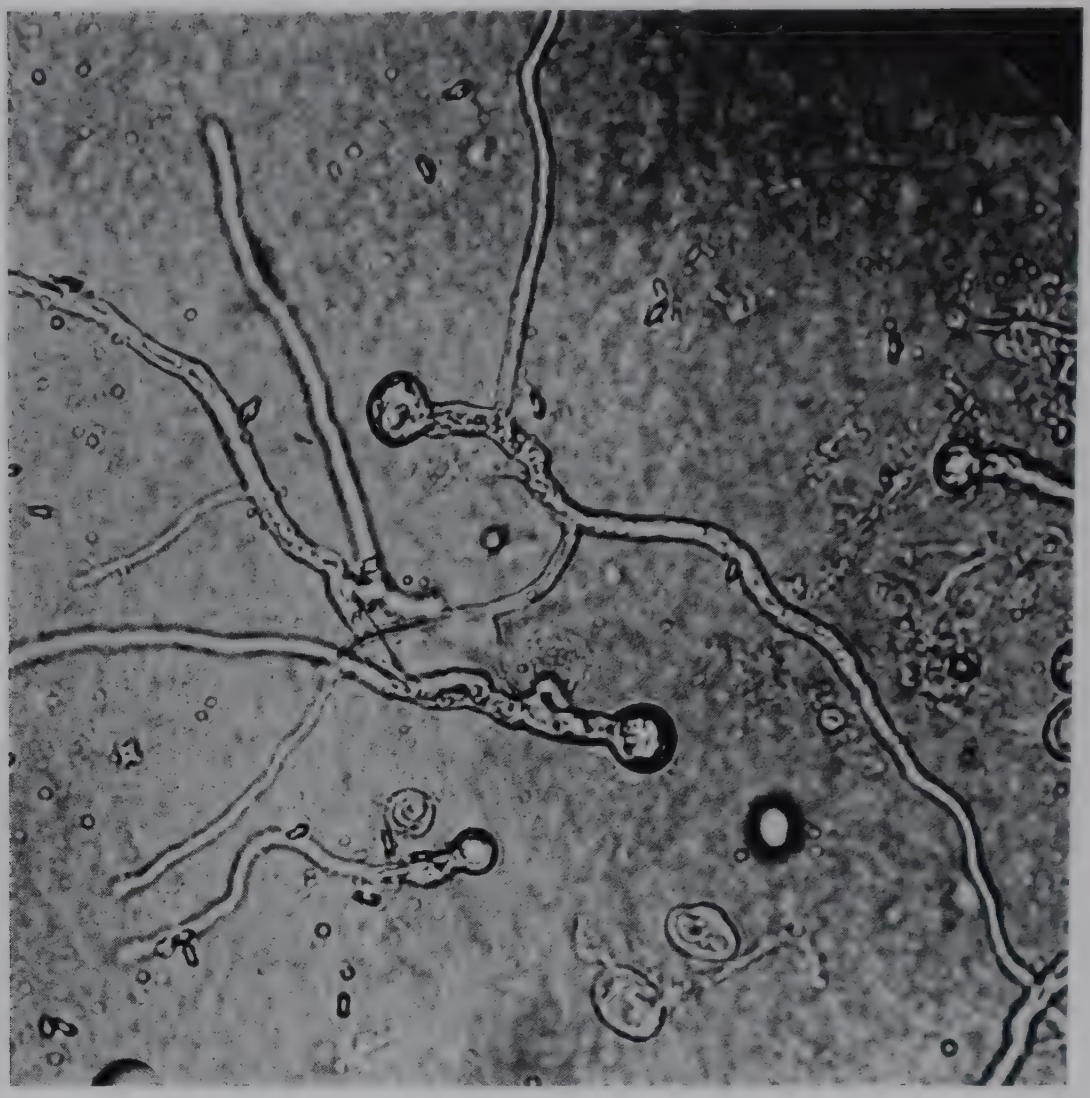

FIG. 91. BLASTOMYCOSIS
Culture mount grown at room temperature. × 600

transient mild symptoms. In the former case, chill, pain in the chest, fever, increased respiratory rate, rapid pulse, cough, and expectoration of blood-tinged sputum are characteristic. The chest signs resemble those of other pulmonary and pleural disorders. The chest films may show, in early cases, no parenchymal lesions. The only finding may be an enlargement of the mediastinal lymph nodes. As a rule, one finds dense masses located near the hilum and projecting into the lung fields with irregular outlines. Cavities are usually not the rule, but when present they are small, irregular, and with hazy out-

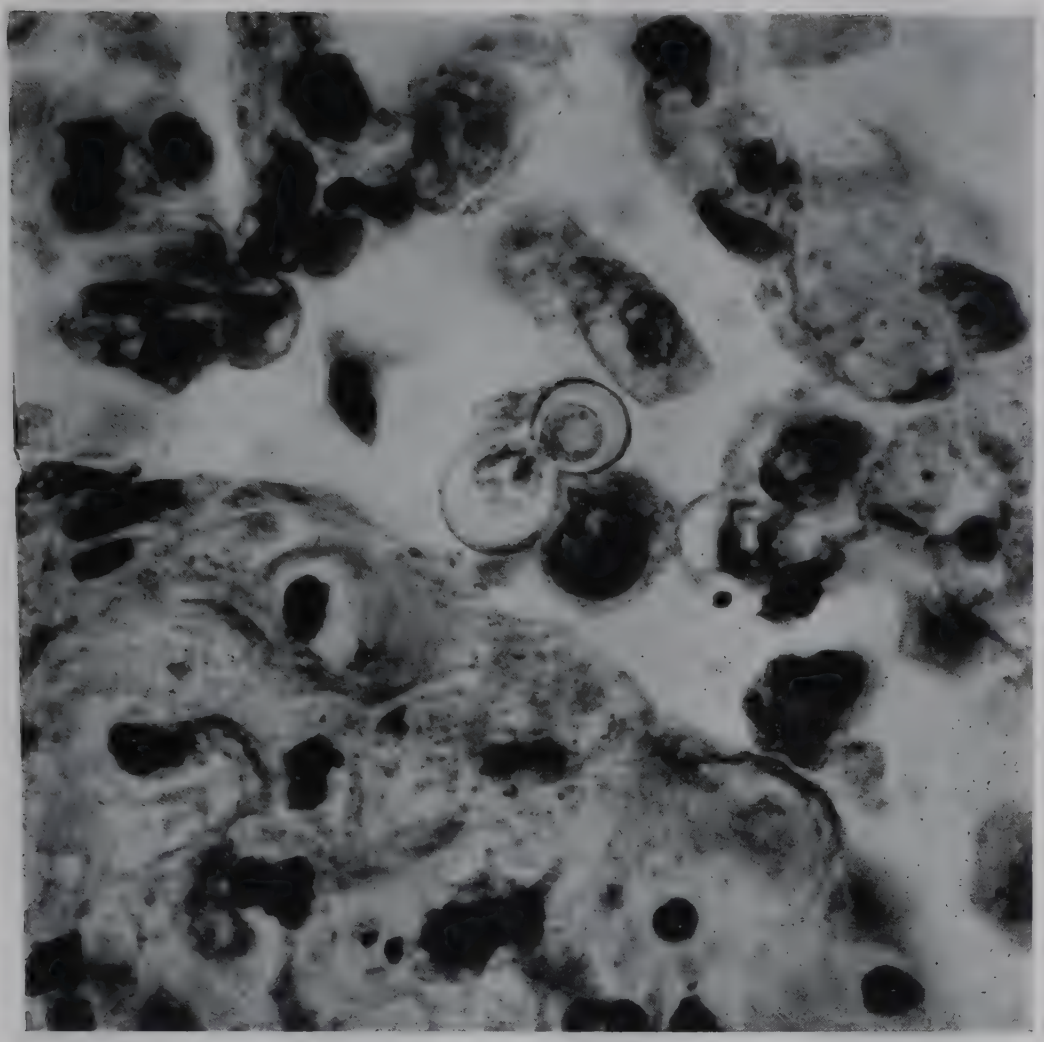

FIG. 92. BLASTOMYCOSIS MICRO-ORGANISM IN TISSUE

lines. In systemic blastomycosis, when the lungs are secondarily involved, the pulmonary shadows may resemble miliary tuberculosis.

Cerebrospinal Blastomycosis. Although a primary form has been reported, this occurs chiefly as a metastatic process secondary to systemic blastomycosis. The clinical manifestations do not differ from those of cerebrospinal infection due to other organisms. The possibility of blastomycetic etiology should always be considered in obscure cerebrospinal disease. Microscopic and culture studies for the presence of Blastomyces and other fungi should be a part of every routine spinal fluid examination.

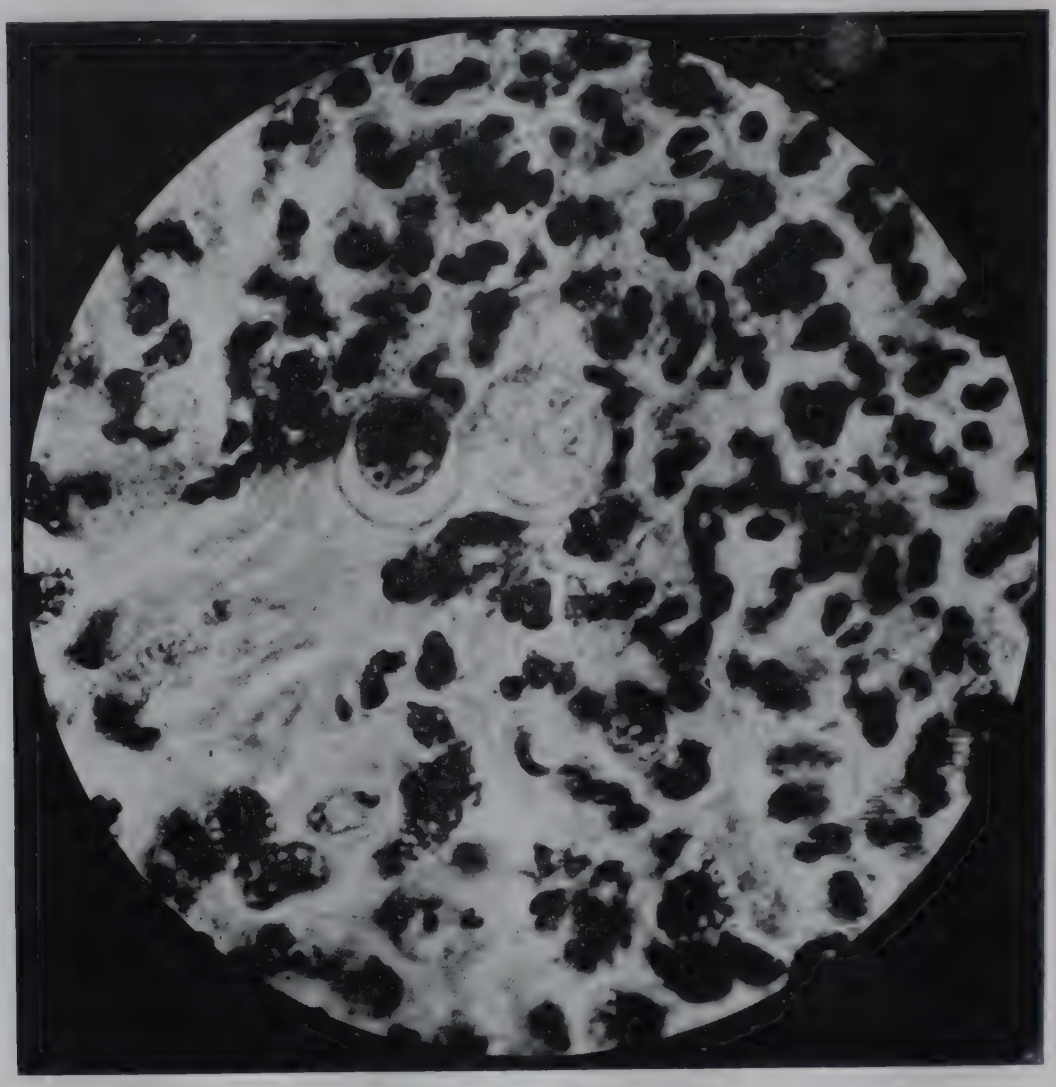

FIG. 93. BLASTOMYCOSIS MICRO-ORGANISM IN TISSUE

The skin and lungs are the organs most commonly affected in systemic blastomycosis. Next in order of frequency are the kidneys, spleen, bones and joints, liver, pleura, lymph nodes, brain, vertebrae, skull bones, prostate, pericardium, meninges, myocardium, endocardium, pancreas, peritoneum, testicles, eyes, adrenals, larynx and trachea, gastro-intestinal tract, bladder, spinal cord, and tongue.

TREATMENT

In the cutaneous type, *surgery* is recommended if the lesion is small. Some cases respond to surgical diathermy or actual

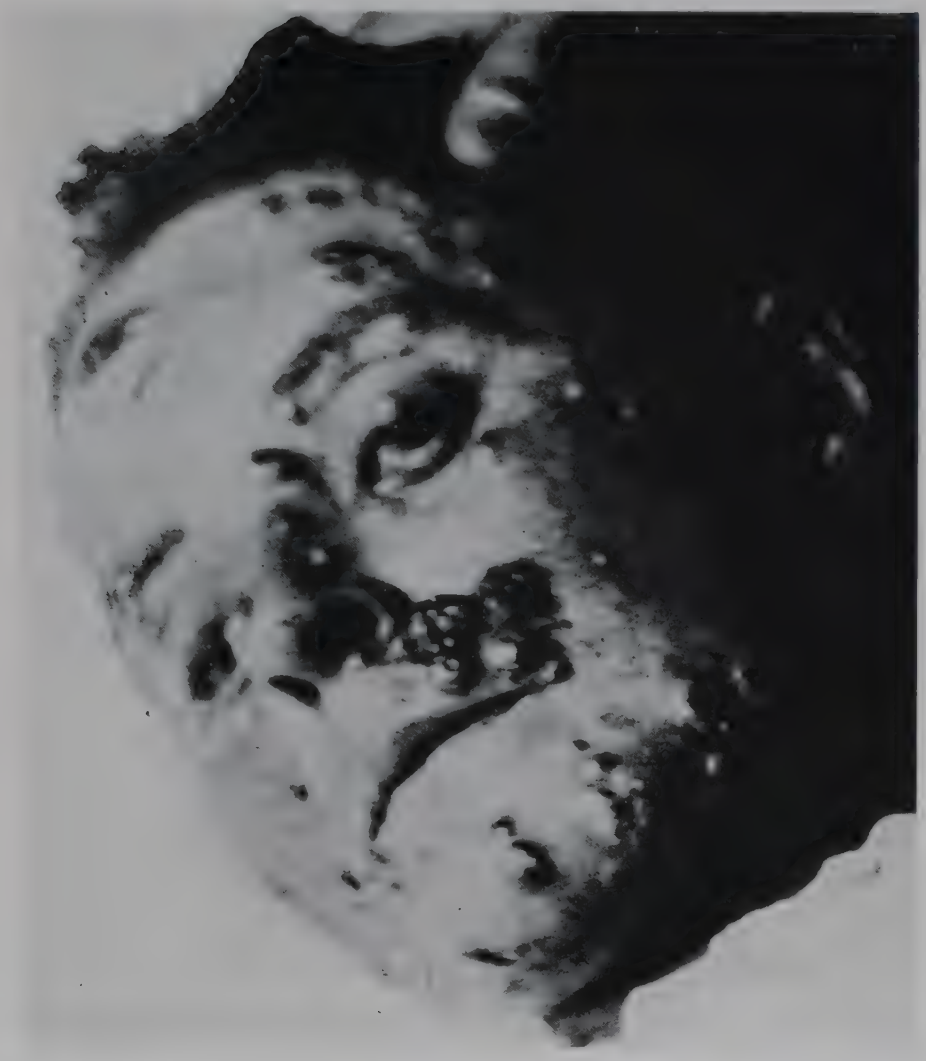

FIG. 94. BLASTOMYCOSIS

cautery. *Roentgen ray* therapy is effective alone or in combination with surgery. The dosage advised is 75 to 100 r filtered through 1 mm. aluminum once a week. It is not advisable to exceed a total dose of 1,200 to 1,500 r. Conant and his associates warn against the use of roentgen ray therapy in patients with hypersensitivity to blastomycin before partial desensitization with injections of blastomycin vaccine has been produced. Saturated solution of potassium iodide can be given orally in large doses just below the level of toxicity. Iodine has been administered intravenously with good results. The use of ethyl iodide inhalations is advised in extensive primary cutaneous blastomycosis and in systemic blastomycosis

with or without cutaneous manifestations, particularly in the presence of pulmonary involvement. The initial dose of 2 cc. is increased by 0.5 cc. per dose until 4 cc. is reached. Treatment should be given on two successive days and omitted on the third. Martin and Smith suggest desensitization with vaccine before instituting iodide therapy. They recommend the following technic. A skin test with a standardized heat-killed blastomycin vaccine is done by injection intracutaneously of 0.1 cc. of the vaccine. The size of the maximal reaction is determined by observation of the site of injection at intervals of twenty-four and forty-eight hours. A reaction of 1 cm. or more in diameter indicates hypersensitivity. The size of reaction observed determines the dilution of the vaccine required for the first desensitization. A dilution of 1:100 is used for the first injection if the reaction is from 1 to 2 cm. in diameter. A 1:1,000 and 1:10,000 dilution is used for reactions of 2 cm. and 3 cm. in diameter, respectively. The proper dilution is injected subcutaneously, beginning with 0.1 cc. The dose is increased by 0.1 cc. until 1 cc. is reached. Injections are given three times a week. This procedure is repeated with each lower dilution until undiluted vaccine is used. A local or general reaction is a sign to stop injections. These may be resumed several days later with a dilution of one tenth as strong as the one that produced the reaction. Complete desensitization is not to be expected, but a definite reduction in the size of the erythematous reaction takes place, indicating a decrease in hypersensitivity. Specific *vaccino-therapy* has not yet been proved of value, although Stober reported clinical improvement through use of this method. Jacobson recommends intramuscular injections of colloidal copper. The author has had no experience with this form of treatment. Martin reports occasional benefit from the use of *antiblastomyces rabbit serum*. *Sulfonamides* have not proved too effective although several questionably favorable reports have appeared in the literature. Noojin and Callaway found that the inhibition of growth of

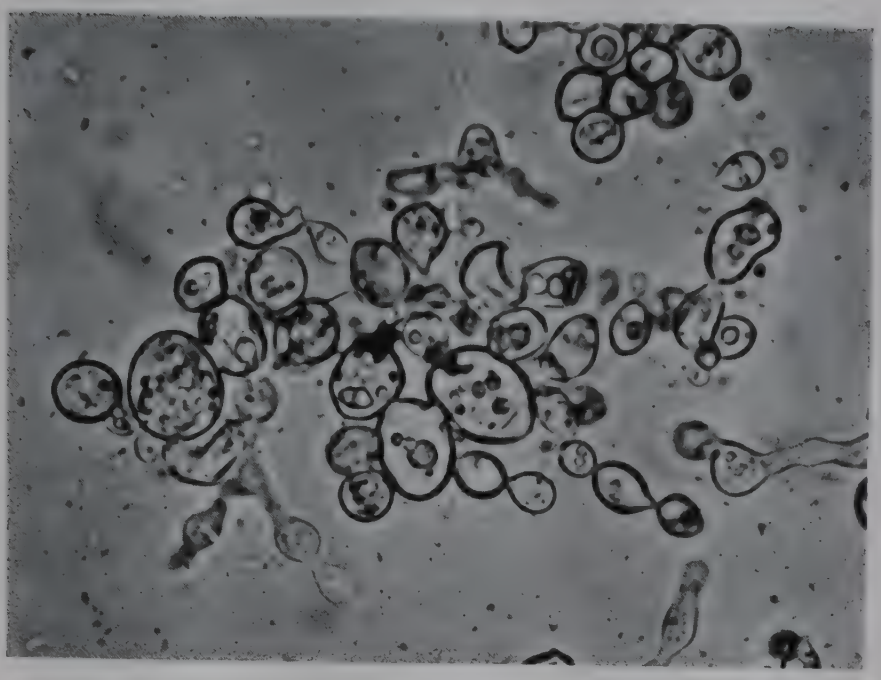

FIG. 95. BLASTOMYCOSIS BRASILIENSIS

Culture mount from beef infusion glucose agar, 37 C. × 600. (Courtesy of Conant et al.)

Blastomyces dermatitidis in vitro required concentrations well above the maximum clinical drug levels tolerated. They therefore concluded that sulfonamide compounds are not practical if used orally and parenterally. *Streptomycin* and *penicillin* have thus far proved of doubtful therapeutic value in the treatment of this disease. Myers and Ordal have shown that Blastomyces dermatitidis was sensitive to gliotoxin in vitro but that the drug was extremely toxic to the chick embryo.

Whatever form of therapy is adopted, sunshine and a high caloric diet, especially in systemic blastomycosis, are a vital necessity.

PARACOCCIDIOIDES (BLASTOMYCES) BRASILIENSIS (SPLENDONE; DE ALMEIDA, 1930)

This organism causes the disease known as paracoccidioidal granuloma (South American blastomycosis), reported from

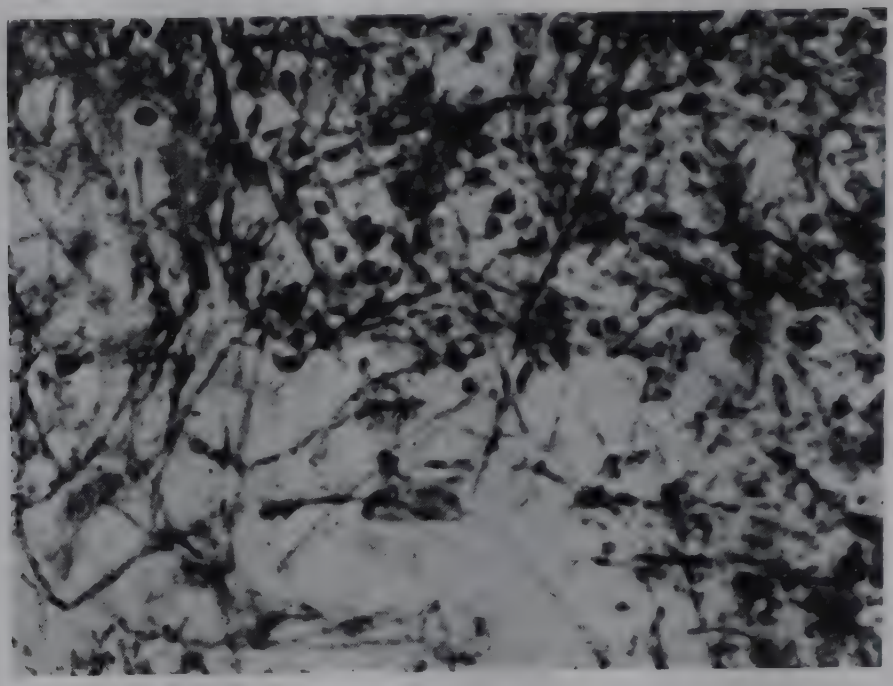

FIG. 96. BLASTOMYCOSIS BRASILIENSIS

Culture mount grown at room temperature. × 600. (Courtesy of Conant et al.: Manual of Clinical Mycology, W. B. Saunders Co., 1944; p. 82, Fig. 42 C)

Brazil by Lutz in 1908. Although it has not yet been reported in this country, it is included in the discussion here, since the clinical picture is similar in some respects to that of blastomycosis caused by Blastomyces dermatitidis as well as to that of coccidioidal granuloma (see pp. 146, 148).

MYCOLOGY

Paracoccidioides brasiliensis appears in the tissue or pus as single- or multiple-budding thick-walled yeastlike cells. The buds are excessively small—coccoid, in fact. The single-budding cells, from 10 to 30 microns in diameter, are similar to those seen in the organism causing Gilchrist's disease. The multiple-budding cells, as large as 60 microns in diameter, are diagnostic for this disease. Buds of 1 micron or more in diameter may be attached to and surround the parent cell.

Diagnosis is made by direct microscopic examination of material from the lesions. Crusts, scrapings from the lesions,

FIG. 97. MUCOCUTANEOUS SOUTH AMERICAN BLASTOMYCOSIS
(Courtesy of de Almeida: Mycologia Medica, Companhia Melhoramentos de São Paulo, Brasil, 1939; Fig. 121)

and pus should be placed in 10 per cent potassium hydroxide and examined under a cover glass. Cultures should be made on Sabouraud's glucose agar and beef infusion or blood agar at both room temperature and at 37 C. On Sabouraud's agar at room temperature, the primary culture may remain heaped, compact, cerebriform (similar to Achorion schoenleini) and show, microscopically, several budding forms identical with those seen in lesions. These cultures become filamentous after some time and develop a short nap of white aerial mycelium.

On blood agar at 37 C., the cultures remain yeastlike, waxy, and composed of the same type of single- and multiple-budding forms as are seen in the lesions.

CLINICAL MANIFESTATIONS

The individual lesions are clinically and histologically similar to those of Gilchrist's disease and coccidioidal granuloma. Enlargement of the lymph nodes, suggesting Hodgkin's disease, is the most characteristic single clinical finding in all cases of South American blastomycosis. De Almeida and other South American workers classify the disease as follows: (1) Muco-cutaneous form; (2) lymphangitic form; (3) visceral form.

The *muco-cutaneous* form. The primary lesions usually occur either on the skin around the mouth or nose, or on the mucosal surface of the tongue, gums, cheek, lips, or nose. On the mucosa, the primary lesion is usually a small papule which soon ulcerates, enlarging peripherally and into the deeper structures. New lesions continue to appear until there is extensive involvement which may result in complete destruction of the epiglottis, vocal cord, and uvula. The regional lymph nodes become enlarged and undergo necrosis and finally rupture through the skin, giving rise to permanent draining sinuses. The lymph nodes in the axillary and inguinal areas may become similarly involved as a result of the dissemination of the micro-organism through the blood stream. The lesions are painful and cause considerable difficulty in swallowing, resulting in malnutrition. Death is usually the result of starvation and terminal pyogenic infection. The cutaneous lesions are granulomatous and may or may not ulcerate.

The *lymphangitic* form is characterized by massive lymph node enlargement, particularly in the neck region. The overlying skin becomes secondarily involved when the lymph nodes become necrotic and drain through the skin.

In the *visceral* form the portal of entry is believed to be the gastro-intestinal tract with ultimate dissemination of the infec-

tion resulting in involvement of the spleen, liver, and other organs. Abdominal pain, severe gastro-intestinal disturbances including anorexia and vomiting may be present. The presence of abdominal pain helps to differentiate this disease from granuloma coccidioides since the intestinal tract is not involved in the latter. Lung involvement is usually secondary and is present in about 20 per cent of the patients with the visceral type of infection.

TREATMENT

The disease may run either an acute or a chronic course, and almost always terminates fatally. Few verified cures have been reported. Iodide therapy has been reported effective in some cases by de Almeida. The mode of administration is the same as that for North American blastomycosis. Sulfonamides have been reported effective if given over a long period.

Histoplasma Capsulatum (Darling, 1906)

In 1906 Darling described the organism Histoplasma capsulatum and the postmortem findings in 3 cases of histoplasmosis. In 1912 Da Rocha Lima expressed the view that Histoplasma capsulatum is closely related to Cryptococcus farciminosus, the etiologic organism in epizootic lymphangitis occurring in horses. In 1933 De Monbreun discovered that the organism could be cultured and grown in yeastlike and mycelial form. By reproducing the disease in monkeys by intravenous inoculation, he further identified the fungus as the etiologic agent of histoplasmosis. Since then several cases in both adults and infants have been reported.

MYCOLOGY

The organism is small, encapsulated, oval-shaped, and from 1 to 3 microns in length. It is usually found in the mononuclear cells in peripheral blood smears, sternal bone marrow smears, sections of spleen, also in biopsy sections of skin and lymph nodes, and in blood cultures. In sections of the tissue

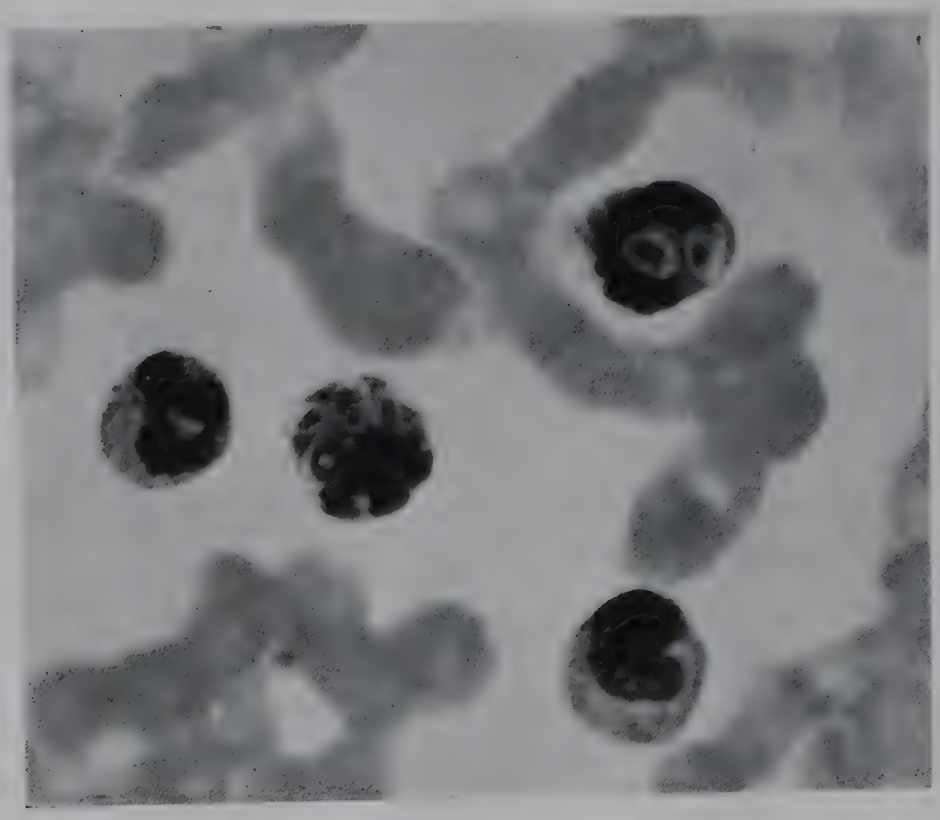

FIG. 98. HISTOPLASMA CAPSULATUM
Bone marrow smear with organisms in polymorphonuclear nucleus. × 1300.
(Courtesy of Conant et al.)

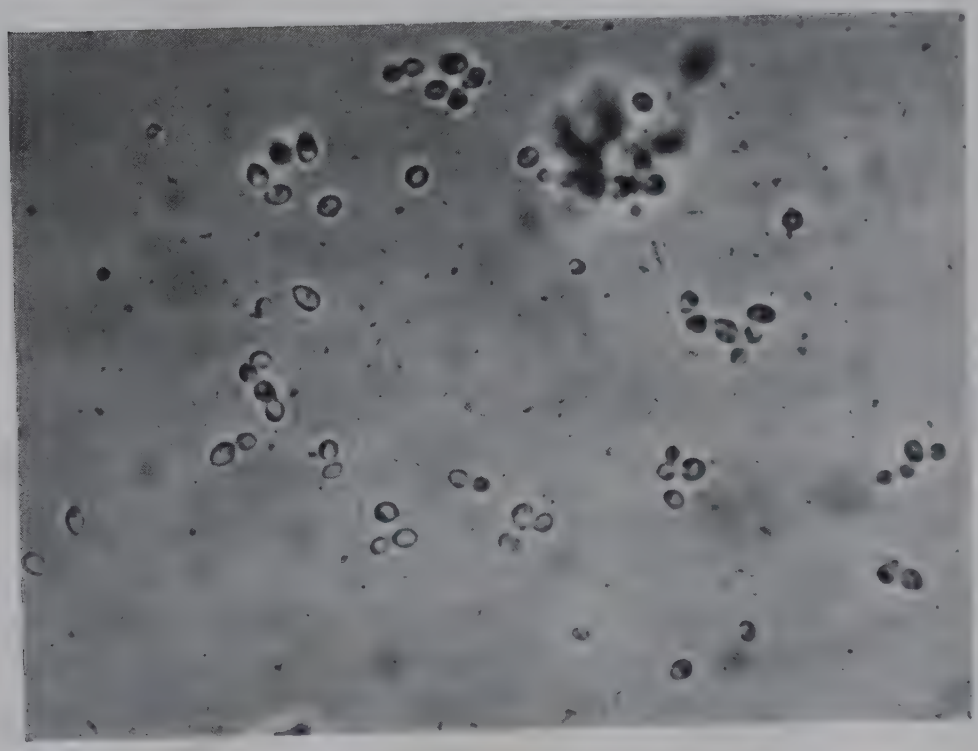

FIG. 99. HISTOPLASMA CAPSULATUM
Culture mount from blood agar at 37 C. × 700

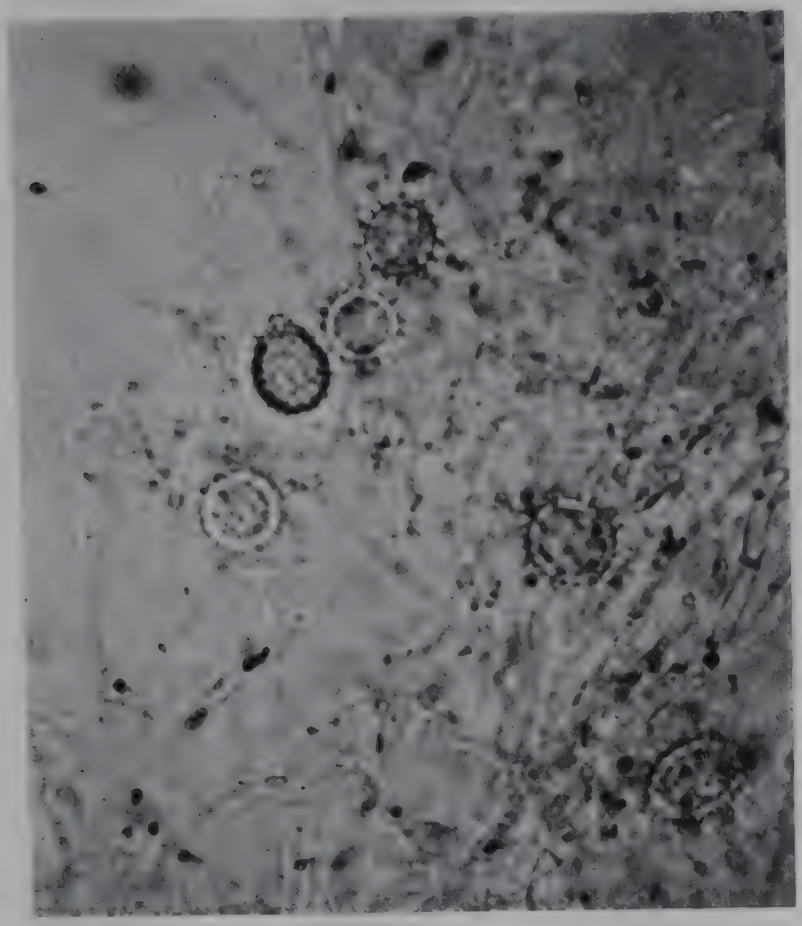

FIG. 100. HISTOPLASMA CAPSULATUM

Culture mount on Sabouraud's medium at room temperature (Courtesy of Conant: J. Bacteriol. 41: 577, 1941; Fig. 3, Plate 11)

suspected and stained after Bensley's procedure, the parasites appear stained deep red.

The organism may be cultured on Sabouraud's media or in sealed blood agar tubes. On Sabouraud's media and grown at room temperature, the growth is moldlike. On culture mount one sees large warty thick-walled chlamydospores attached to the fungus filaments. The growth on sealed blood agar tubes at 37 C. is yeastlike. On culture mount one sees budding and nonbudding yeastlike cells.

CLINICAL MANIFESTATIONS

The clinical picture described by Darling comprises emaciation, weakness, pyrexia, anemia, leukopenia, and splenomegaly.

Variations in the symptomatology have been reported, with some of the above named symptoms lacking. In children the first evidence of the disease may be in the gastro-intestinal tract with nausea and diarrhea. Henderson, Pinkerton, and Moore found ulcerative enteritis as the chief lesion in their case. Lymphadenopathy is present, including the mesenteric lymph nodes, but this finding is more marked in adults than in children. The lungs may be either primarily or secondarily involved. Pulmonary involvement is the rule in generalized cases. Bone lesions, enlargement of the liver, as well as adrenal involvement, have been reported. Skin findings varying from a dusky erythema to purpuric spots or to urticarial lesions have been recorded. Ulcerative lesions of the skin, tongue, nasopharynx, or larynx have also been reported. It is advisable to consider histoplasmosis in the differential diagnosis of any obscure case of splenomegaly, especially if the splenomegaly is associated with intermittent pyrexia, cachexia, and leukopenia.

Palmer, Christie, and Peterson believe that there is prevalent in certain parts of the country a mild subclinical infection with H. capsulatum from which recovery takes place. They base their claim on the finding of pulmonary calcification in patients showing negative reactions to tuberculin and coccidioidin and positive reactions to histoplasmin. They recognize, however, that cross sensitization with blastomycin and coccidioidin may exist.

Cutaneous reaction to histoplasmin in infected individuals may be tuberculin-like (delayed) and immediate.

On *pathologic* examination, one finds in the spleen, liver, lungs, and intestines, as well as in other tissues, gray and white nodules. Involvement of the mesenteric lymph nodes is the rule. The lesions are necrotic, not unlike those seen in tuberculosis. The fungus is found in the fixed reticulo-endothelial cells in the spleen and liver, whereas in other parts of the body it may be found in the phagocytic cells.

TREATMENT

No specific therapy has been given sufficient trial in this disease, because diagnoses usually have been made after necropsy. In the few cases recognized before death and treated, results have been unsatisfactory. The following treatments have been reported: ionized copper, massive doses of potassium iodide, local x-ray treatment and sulfonamides. The therapeutic results reported with the use of penicillin have not been favorable. Meleney recommends the antimony preparations such as antimony sodium tartrate, the trivalent organic compound such as fuadin, or the pentavalent preparation such as neostam. Mantel, Troy, and Kendall report clinical improvement in one case treated with neostam.

Rhinosporidium Seeberi

This micro-organism is the cause of rhinosporidiosis, a rare mycotic disease with a predilection for the mucous membrane of the nose. The eyes, ears, larynx, and occasionally the vagina, penis, and skin may become involved. The disease occurs spontaneously in cows, horses, and mules.

MYCOLOGY

Direct microscopic examination of material from the polypoid masses reveals round to ovoid spores 7 to 9 microns in diameter, and spore-filled sporangia. The sporangia are large (up to 250 to 300 microns in diameter). Slides from biopsy section stained with hematoxylin and eosin show the large thick-walled sporangia filled with endospores as well as empty ones. Ruptured sporangia and endospores scattered about on the epithelial surface or throughout the tissue may also be seen.

The cultural characteristics of this fungus are not known since it does not grow on ordinary laboratory media.

CLINICAL MANIFESTATIONS

The nose, especially the anterior nares, is the most common site of infection. Occasionally it spreads to other sites on the

face, to the posterior pharynx and larynx. The large polyps may produce nasal obstruction, dyspnea, and dysphagia. The infection may begin as a mucoid discharge and severe itching. The lesions develop slowly, are sessile on the mucosa, but as the tumor masses develop they become pedunculated. The fully developed swellings are globoid or polypoid and may eventually weigh up to 20 Gm. The color of the lesions varies from pale pink to deep purplish-red; the surface is covered with sticky mucus. Older lesions become verrucous and may resemble a

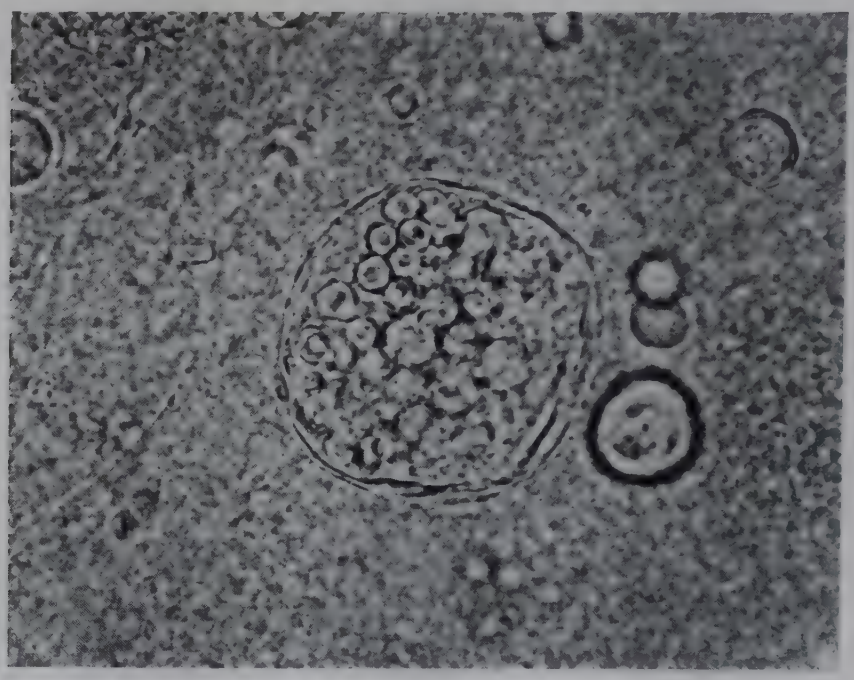

FIG. 101. COCCIDIOIDES IMMITIS IN PUS. × 490
(Courtesy of Dubos: from Bacterial and Mycotic Diseases of Man, J. B. Lippincott Co., 1948; Page 618, Fig. 71)

cauliflower. In a small number of cases the eye may become involved. The bulbar, as well as the palpebral conjunctiva, may be affected. The ear lesions resemble ordinary aural polyps. The penile lesions resemble venereal warts which slowly change to cauliflower-like growths. Infections in the vagina and rectum resemble condylomata, hemorrhoids, or rectal polypi. The disease is usually not fatal.

Treatment. The superficial and early lesions may be removed by careful dissection or electrodesiccation. In the extensive cases, pentavalent antimony is recommended as an adjunct to surgical measures.

Coccidioides Immitis

This organism, which causes coccidioidomycosis, was described

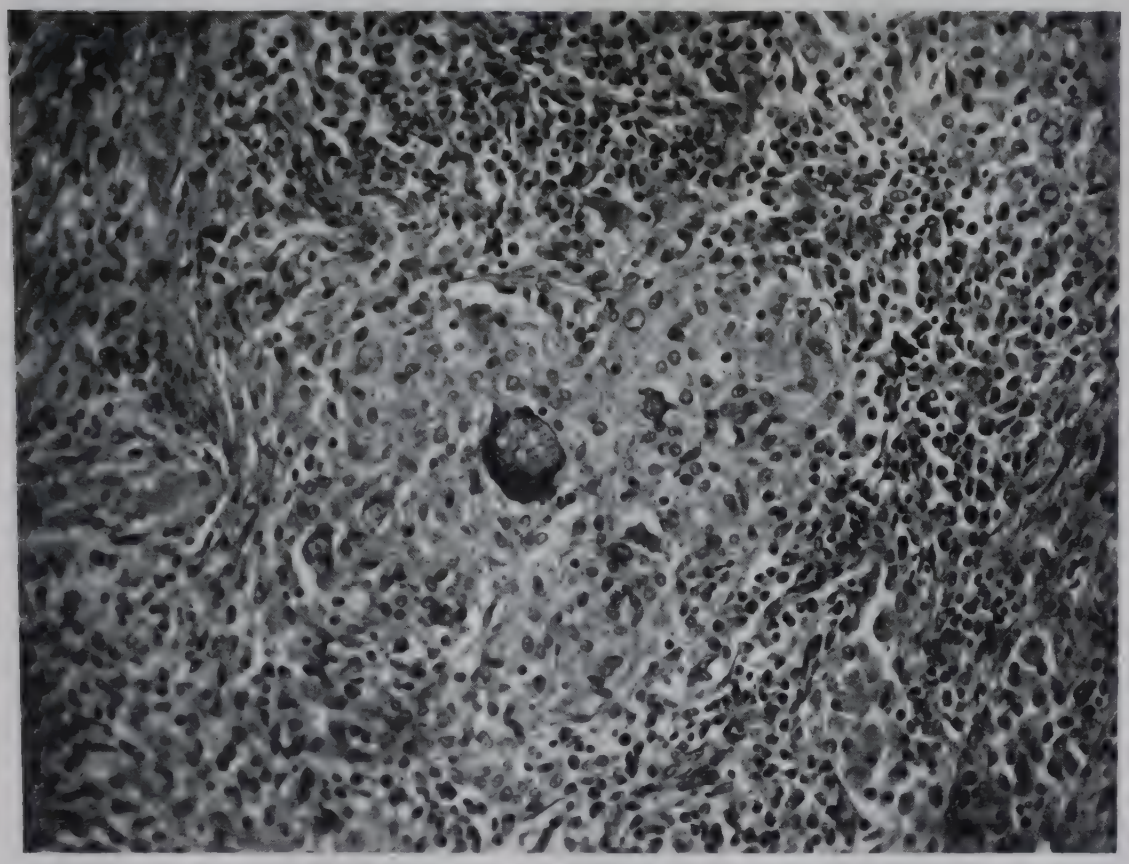

Fig. 102. Coccidioides Immitis in Tissue. × 200

first by Wernicke, who reported it from Buenos Aires in 1891. Three years later Rixford reported from San Francisco the first case of it in this country. Ophuls in 1900 reported the second case, and suggested naming the organism Oidiumcoccidioides. Since then numerous reports on it have appeared in the literature, most of the cases occurring in California.

MYCOLOGY

Microscopically, coccidioides immitis may be demonstrated in the pus of an unopened and uncontaminated lesion; occasionally it is demonstrable even in the discharges from opened

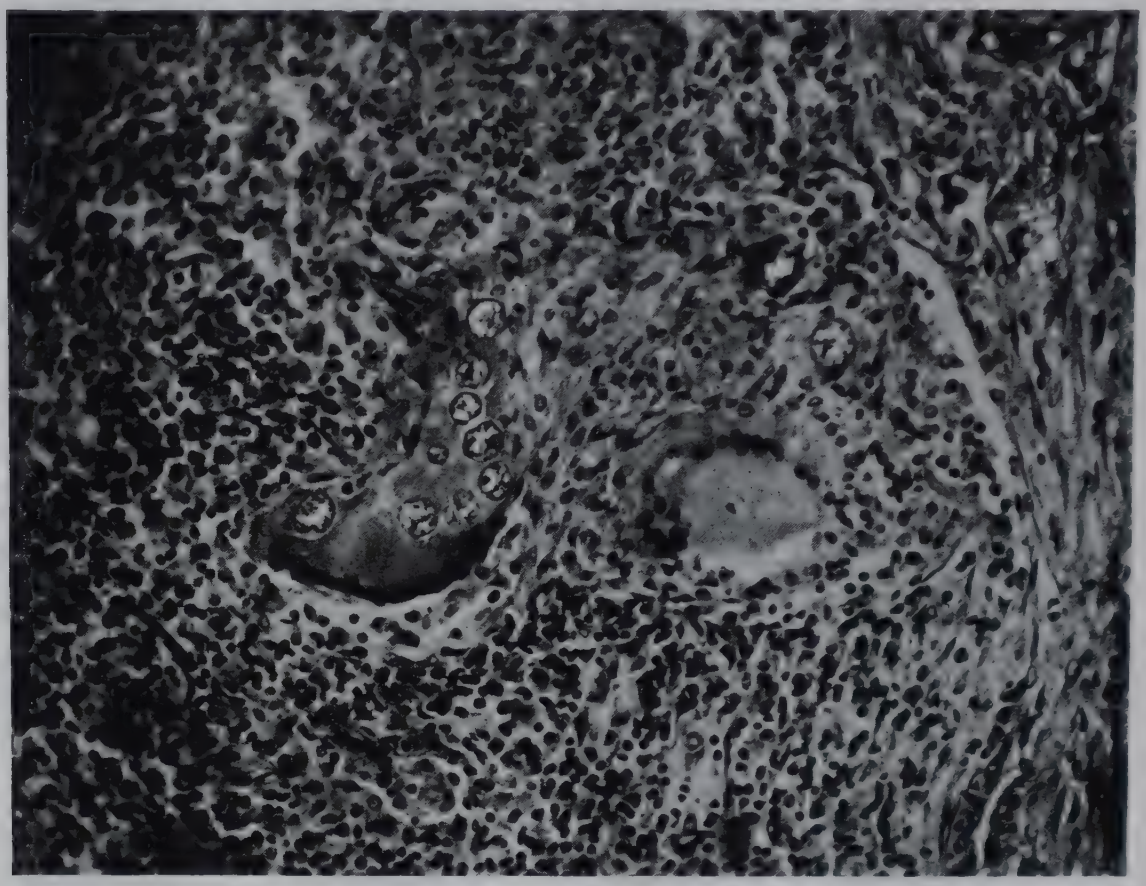

FIG. 103. COCCIDIOIDES IMMITIS IN TISSUE. × 400

and contaminated sinuses, ulcerations, and abscesses, and in sputum. In pus, spinal fluid, and tissue, it can be identified by its characteristic spherical shape and double-contoured capsule, which varies in size from 5 to 60 microns. The protoplasm is granular. Under sufficient magnification, granules that have matured are seen to be exact replicas of the parent organism, appearing as a central deeply stained mass of protoplasm surrounded by a spherical double-contoured capsule. In the tissue and pus, reproduction takes place by endosporu-

lation. Jacobson states that he has seen evidence of budding. Lactophenol–cotton blue or Mallory's eosin and methylene blue stain may be used; the former stains the parasite blue, the latter gives a blue protoplasm and a red capsule.

Any of the sugar media is suitable for culture, the medium of choice being Sabouraud's maltose peptone agar. Although

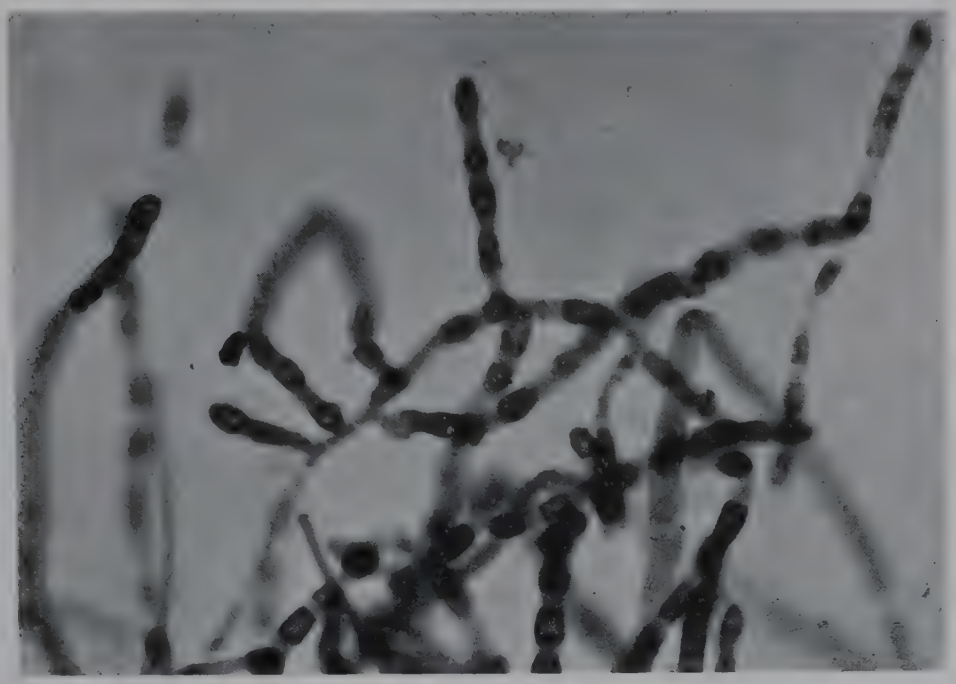

FIG. 104. COCCIDIOIDES IMMITIS

Culture mount grown on Sabouraud's medium at room temperature, showing thick-walled arthrospores. × 730 (Courtesy Dubos: from Bacterial and Mycotic Diseases of Man, J. B. Lippincott Co., 1948; Page 617, Fig. 70)

room temperature is usually sufficient, growth is best under aerobic conditions and at body temperature. It usually begins within ten days of planting. The growth at first is moist and membranous, but the colony soon develops an abundant cottony aerial mycelium which is white at first but becomes brownish with age. On culture mount, one sees branching septate hyphae which break up into thick-walled arthrospores which may be rectangular, ellipsoidal, or spherical. Animal inoculation is necessary for identification of the organism in its cultural form. Laboratory workers should wear masks while

working with cultures of this micro-organism since the arthrospores are highly infectious.

ANIMAL INOCULATION

All laboratory animals are susceptible. Guinea pigs and mice are most commonly used. Aspirated pus from the infected areas shows endospores surrounded by a spherical double-contoured capsule.

FIG. 105. PULMONARY COCCIDIOIDOMYCOSIS, SHOWING MASS WHICH WAS AT FIRST MISTAKEN FOR TUMOR OF THE LUNG

IMMUNOLOGIC REACTION

Although the reaction to coccidioidin is specific, it does not necessarily establish the diagnosis of any given infection, since the reaction may remain long after the infection has apparently subsided. Lewis and Hopper tested 200 patients with no evidence of coccidioidomycosis and found a negative reaction in 100 per cent. The presence of agglutinins, precipitins, or com-

plement fixation bodies in the blood of infected persons has not been definitely proved.

CLINICAL MANIFESTATIONS

The disease appears to be especially prevalent among the working classes; agricultural laborers and grape pickers are particularly susceptible. Males are predominantly affected, the highest incidence being between the ages of 20 and 45, although no age group is immune. The majority of cases originate in the San Joaquin Valley and Los Angeles County, California. Scattered cases have been reported in the Middle and Southern States. One of the authors (J. H. S.) has recently seen a case originating in Arizona. This patient has never lived in California.

There are two stages: the acute phase known as valley fever and that of chronic or coccidioidal granuloma. Primary infection by way of the respiratory tract is common, usually resulting from inhalation of dust containing the fungus. The symptoms of primary pulmonary coccidioidomycosis resemble those of a mild upper respiratory infection, although at times the onset is marked by malaise, chills, fever, anorexia, cough, headache, backache, night sweats, and pleuritis. Chest signs are not usually present except in the more severe cases. In such cases there may be dullness and suppressed breathing sounds and rales. The roentgenogram of the chest may show soft, fuzzy, hilar thickenings, pneumonic type of infiltration, isolated nodular lesions in the parenchyma of the lung, or small pleural effusions. More than one of the above types of findings may be seen in a single patient. The incubation period lasts from eight to fourteen days, sensitivity to the fungus usually developing within a period of from three to twenty-one days. Hypersensitivity is manifested by the appearance of erythema nodosum or erythema multiforme. This acute form of the infection, known as valley fever, San Joaquin fever, or desert rheumatism, subsides without complications. The secondary

phase—coccidioidal granuloma—develops by dissemination from the primary focus either at the time of or after the initial infection. Symptoms during this phase are indistinguishable from those of tuberculosis, and lesions may appear in the skin, bones, joints, lymph nodes, lungs, larynx, adrenals, and elsewhere except the intestines. This phase of the disease is almost always fatal.

FIG. 106. CHROMOBLASTOMYCOSIS; BODIES IN PUS. × 825

(Courtesy of Conant et al.: Manual of Clinical Mycology, W. B. Saunders Co., 1944; Page 99, Fig. 51)

Cutaneous Coccidioidomycosis. The cutaneous and subcutaneous lesions may be primary or secondary and may take any of several forms. They may appear as ulcerative nodules arising in the epidermis and extending later to subcutaneous tissue, or they may arise in the latter. They may simulate deep ab-

scesses, tuberculous lesions, or gummata of the skin. Still another type is the soft elastic flesh-colored flaccid tumor that seldom ulcerates. There is also observed a scrofulodermatous lesion that originates in the superficial lymph nodes and is most frequently found in the supraclavicular region and elsewhere in the neck.

FIG. 107. HORMODENDRUM PEDROSOI, "PHIALOPHORA TYPE"

Osseous Coccidioidomycosis. Primary involvement is rare. In the systemic cases, however, secondary osseous invasion is frequent. The most commonly affected parts are the bones of the foot, the ankle joint, ribs, and vertebral column. The

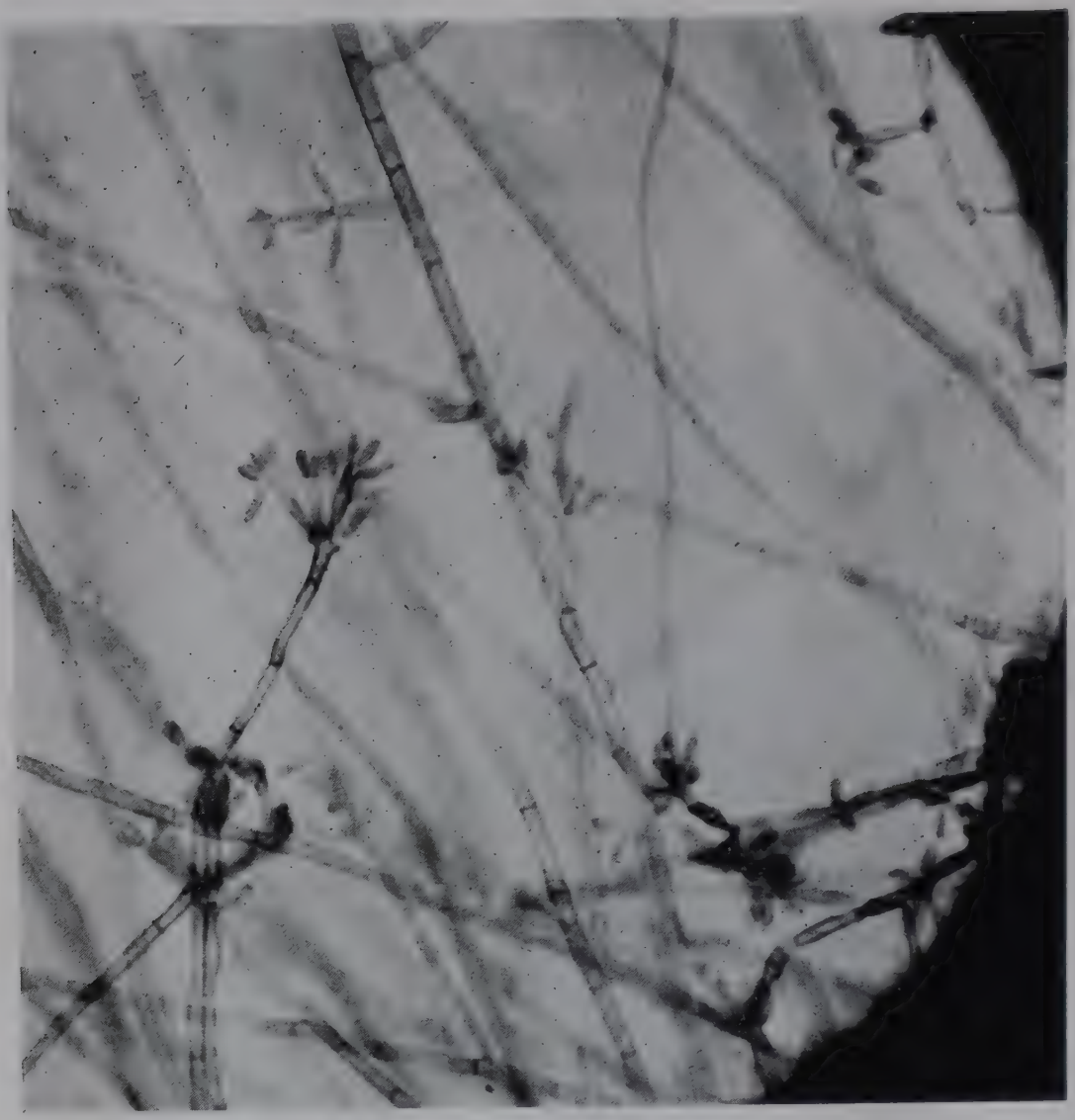

FIG. 108. HORMODENDRUM PEDROSOI, "HORMODENDRUM TYPE"

process usually takes a destructive, osteomyelitic form. In the late stages, bone proliferation is present.

Cerebrospinal Coccidioidomycosis. This is usually a terminal phase of the systemic form of the disease. It is so varied, both in nature and extent, that the physician is confronted with a clinical picture ranging from that of a cerebral or spinal neoplasm to that of an epidemic or other form of meningitis.

TREATMENT

No specific treatment has been evolved. In the *primary pulmonary* type, the object of treatment is to afford the patient

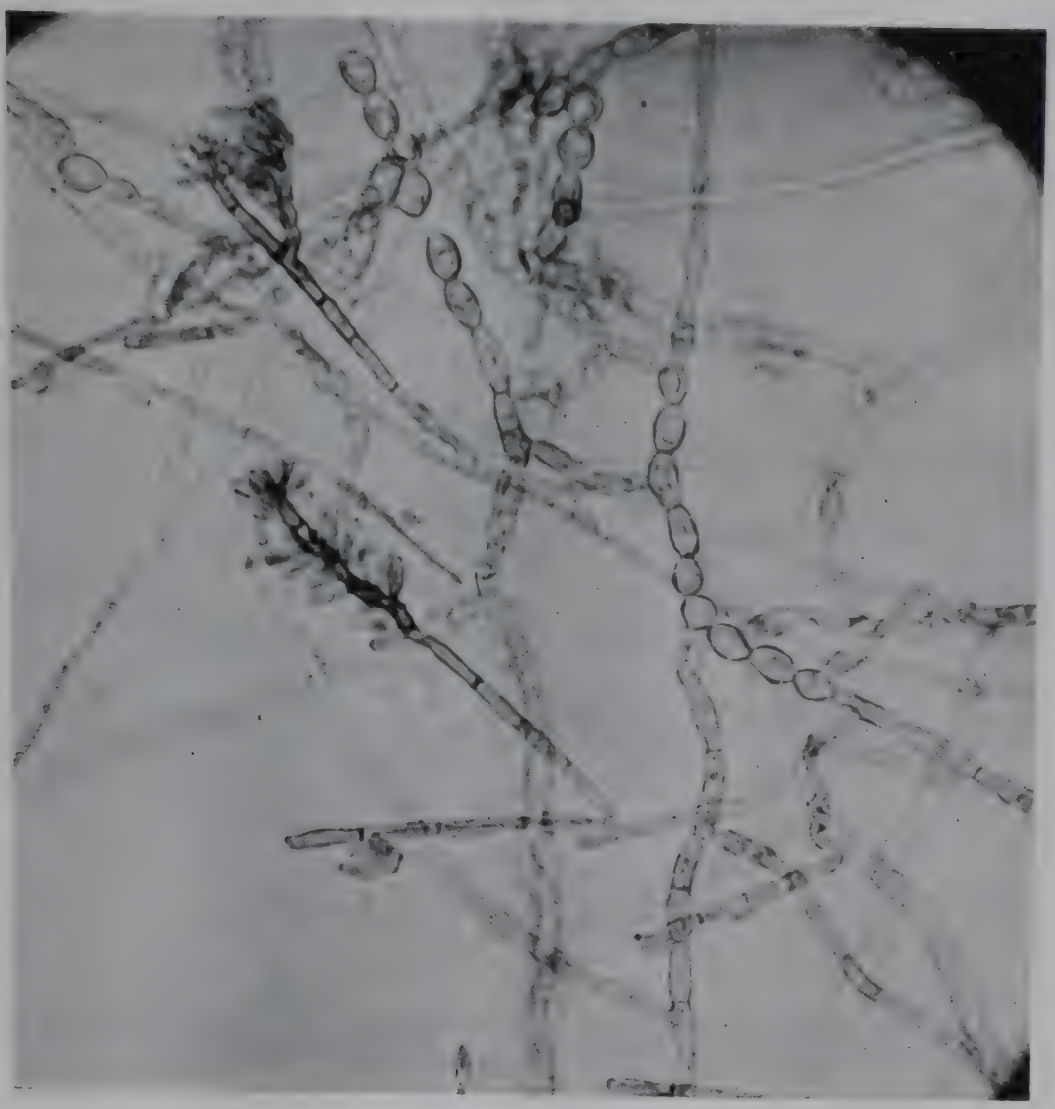

FIG. 109. HORMODENDRUM PEDROSOI, "ACROTHECA TYPE"

optimum condition for localizing the infection. Rest in bed is necessary until the temperature, white-cell count, and sedimentation rate are normal, and the pulmonary lesions have regressed completely or become stationary. Symptomatic treatment such as salicylates with or without codein may be administered. Supportive treatment is essential. The variety of drugs used in the past, including the more recently tried *sulfonamides* and *penicillin*, have not proved too effective in the treatment of the *granulomatous* or *progressive* type. *Vaccinotherapy* has been described as effective, but the reports are few. *Roentgen ray* treatment gives temporary relief. *Iodides* are of

questionable efficacy. In some cases, the therapeutic use of certain drugs is helpful. *Colloidal copper* may be administered intramuscularly in doses of 5 cc. every four to seven days. *Gentian violet* can be given locally in a 1 per cent aqueous solution or intravenously in a 0.25 per cent solution. Since this drug is toxic, no total dose greater than 5 mg. of the drug per kilogram of body weight should be given. *Antimony* and *potas-*

FIG. 110. PHIALOPHORA VERRUCOSA

sium tartrate in a 1 per cent solution may be administered intravenously in doses of 2 to 8 cc. *Thymol* dissolved in olive oil, dispensed in capsule form, is given in daily doses of 1 to 6 Gm. Locally this remedy is applied as a 33⅓ per cent solution in olive oil.

FIG. 111. HORMODENDRUM COMPACTUM. × 816

(Courtesy of Zinsser: Textbook of Bacteriology, Appleton Century and Crafts, New York, 1948; Page 877, Fig. 214)

CHROMOBLASTOMYCETIC FUNGI

The following are the organisms chiefly identified with the disease known as chromoblastomycosis:

Phialophora verrucosa
Hormodendrum pedrosoi
Hormodendrum langeroni
Hormodendrum compactum

These organisms are the chief among the twenty-eight different fungi that have been described as causing the disease.

MYCOLOGY

The above-mentioned causative micro-organisms produce identical forms in tissue. On direct microscopic examination

FIG. 112. CHROMOBLASTOMYCOSIS

(Courtesy of Martin et al.: Am. J. Trop. Med. 16: 1936; Plate 1)

of the pus and tissue, brown thick-walled uni- to multilocular cells are found. In old, necrotic lesions filaments may be seen. On Sabouraud's agar, the colonies are dark green to black, velvety, and show aerial mycelium and concentric rings.

CLINICAL MANIFESTATIONS

At onset, the eruption in chromoblastomycosis takes the form of reddish, purplish, or brownish nodules, or appears as a

deep verrucous or ulcerative lesion. After many months or years, the nonverrucous nodules coalesce and become verrucous, forming large cauliflower tumors. Secondary pyogenic infection takes place. A foul discharge is present. Healing results in scarring. Nonwarty and nonulcerative lesions have also been reported. The most common sites of the eruption are the lower extremities, although the upper extremities, face, and buttocks have been reported involved. Adenopathy is infrequent except when secondary pyogenic infection is present. The picture can simulate that of blastomycosis, tuberculosis verrucosa cutis, psoriasis, and discoid lupus erythematosus. No instances of internal metastasis have been reported. Weidman states that the infection is usually of exogenous origin and spreads by extension.

TREATMENT

Administration of large doses of iodides, in combination with roentgen rays, has been reported as the most successful therapeutic measure. In localized involvement, electrodesiccation and curettage are worth trying. Martin and his associates treated one patient with copper sulfate administered by means of iontophoresis and obtained good results after five months. They used a 1 per cent solution and a galvanic current of 2.5 milliamperes for thirty minutes. Daily treatment was administered. After nine weeks, the current was increased to 10 milliamperes.

Sporotrichum

Numerous species of Sporotrichum are common saprophytes found in all parts of the world on many types of vegetation and in human and animal excreta. In this country, the chief cause of sporotrichosis is Sporotrichum schencki (1910). This organism is pathogenic in such animals as horse and mules, while rats are particularly susceptible. For laboratory purposes the white rat is used.

FIG. 113. SPOROTRICHOSIS

Culture mount of causal organism, showing pear-shaped spores attached to short stalk and to mycelium

MYCOLOGY

It is very difficult to demonstrate the organism in fresh preparations. Lawless uses a stain by which the spores become demonstrable in fresh pus.

The colony grows well on most laboratory media at room temperature. On dextrose agar a recognizable growth is obtained in about five to seven days. The 2-week-old colony is about 2.5 cm. in diameter, moist, and characterized by irregular central convolutions. At first the border is smooth,

FIG. 114. LYMPHANGITIC SPOROTRICHOSIS (PROVED CASE)

later becoming ridged. A light brown at two weeks, the color darkens, except for white surface excrescences, to brownish black; this is an important feature. This characteristic hue is doubtless derived from the spores that darken to a brown or black as the colony ages. Pear-shaped conidia attached to conidiophores and appearing in triads and tetrads are characteristic.

CLINICAL MANIFESTATIONS

Sporotrichosis appears in several different forms.

Lymphangitic Type. This is the most common form in this country. It consists in a primary lesion, usually on the fingers or the hand; this is at first indurated, then softens, breaking

down and forming an abscess. This lesion is frequently called *sporotrichotic chancre.* A week or more later, hard nodules, which later break down, appear along the course of the regional lymphatics. Enlargement of regional lymph nodes is rare. Spontaneous involution of the lesion is not common, and interference is usually necessary.

Other forms manifest *solitary subcutaneous gummatous*

Fig. 115. Sporotrichosis

lesions, or *disseminated subcutaneous gummatous* lesions, with ulceration, or *mixed* lesions that may simulate those of tuberculosis, syphilis, ecthyma, and furunculosis. Associated involvement of the bones, joints, mucous membranes, muscles, and eyes may be present.

The *systemic* phase of the disease may take one form or may represent a combination of the following:

1. *Mucous Membrane Involvement.* Lesions of the cutaneous type appear, involving the conjunctivae and the linings of the nose, tongue, pharynx, mouth, larynx, and intestinal tract.

Involution leaves soft pliable scars, on the surface of which the Sporotricha subsist as saprophytes, making a carrier of the host.

2. *Muscular and Glandular Involvement.* This is usually associated with the cutaneous type of infection. The lesions are characteristically gummatous or simulate the so-called cold abscess.

FIG. 116. ECZEMATOUS SPOROTRICHOSIS (PROVED CASE)

3. *Osteo-articular Involvement.* This may be primary, or it may be secondary to a cutaneous or mucous membrane infection. The osseous involvement may be brought about either by direct extension or by metastasis through the blood stream.

4. *Articular and Synovial Membrane Involvement.* This is not common.

5. *Epididymal Involvement.* This is more frequently seen in laboratory animals than in human clinical manifestations.

6. *Pulmonary Involvement.* Differentiation between this picture and that of tuberculosis, syphilis, and malignant disease is made by laboratory studies.

7. *Gastro-intestinal Involvement.* Extremely rare, this can be diagnosed on the basis of examination and culture of the stools.

8. *Cerebrospinal Involvement.* Extremely rare, this is diagnosed chiefly by the finding of Sporotricha in the spinal fluid.

Allergic lesions (*sporotrichids*), comparable to trichophytids, have been described by De Beurmann.

IMMUNOLOGIC REACTION

De Beurmann, Moore, and Davis state that agglutination reactions are usually demonstrable. Bloch and De Beurmann believe that the intracutaneous test with an extract of Sporotrichum has value. A negative reaction rules out the diagnosis of sporotrichosis. One must be on the alert, however, for the occasional false positive reaction.

TREATMENT

Iodide is the most effective weapon in the treatment of this disease. It is administered as potassium iodide in milk or water orally, beginning with 10 drops of a saturated solution three times a day and increasing by 3 to 5 drops per dose daily until intolerance is reached. This treatment should be continued for at least one or two months after apparent complete recovery. If this drug is not tolerated orally, sodium iodide in daily doses of 1 Gm. may be given intravenously. In the rapidly spreading or fulminating type and in systemic sporotrichosis, it is wise to administer potassium iodide orally and ethyl iodide by inhalation. (The technic and dose are described in the section on moniliasis, p. 53.)

Another method of iodide therapy is by iontophoresis de-

scribed by Shaffer and his associates. This treatment is given daily for a period of thirteen weeks. They recommend a strong solution of iodine U. S. P. diluted 1:100 in isotonic solution of sodium chloride and increased to 1:50 after seven weeks. Since the active ion, iodine, is an anion, the negative electrode is attached to the involved parts and the indifferent positive electrode is placed on the back. They recommend a current of about 15 milliamperes for twenty minutes in the first week and gradually increased to about 35 milliamperes for thirty minutes.

Roentgen ray therapy is indirectly effective because of its action on granulomatous tissue. It is a poor fungicide.

Surgery is the method of choice only if fluctuation is present, when it may be necessary to resort to incision and drainage.

Local application may be made of gentian violet (1 to 2 per cent), potassium permanganate (1:100 or 1:200), or the following ointment:

		Gm. or cc.
℞	Mercurochrome crystals	0.6–1.2
	Aquae	1.2
	Acidi salicylici	2.0
	Petrolati	
	Lanolini aa ad	30.0

℥

Recently good results have been reported in a few instances from the use of *sulfonamides*, but this method of treatment requires further confirmation. *Penicillin* and *streptomycin* have not produced good therapeutic results in this disease.

Although sometimes helpful, the measures described are far from curative in systemic cases.

Actinomyces

Although chiefly Actinomyces bovis is discussed here, other species have been reported as pathogens.

MYCOLOGY

Actinomyces bovis (Hartz; Wolf and Israel) is the chief cause of actinomycosis. Frequently referred to as ray fungus, the micro-organism appears in the pus from draining fistulas

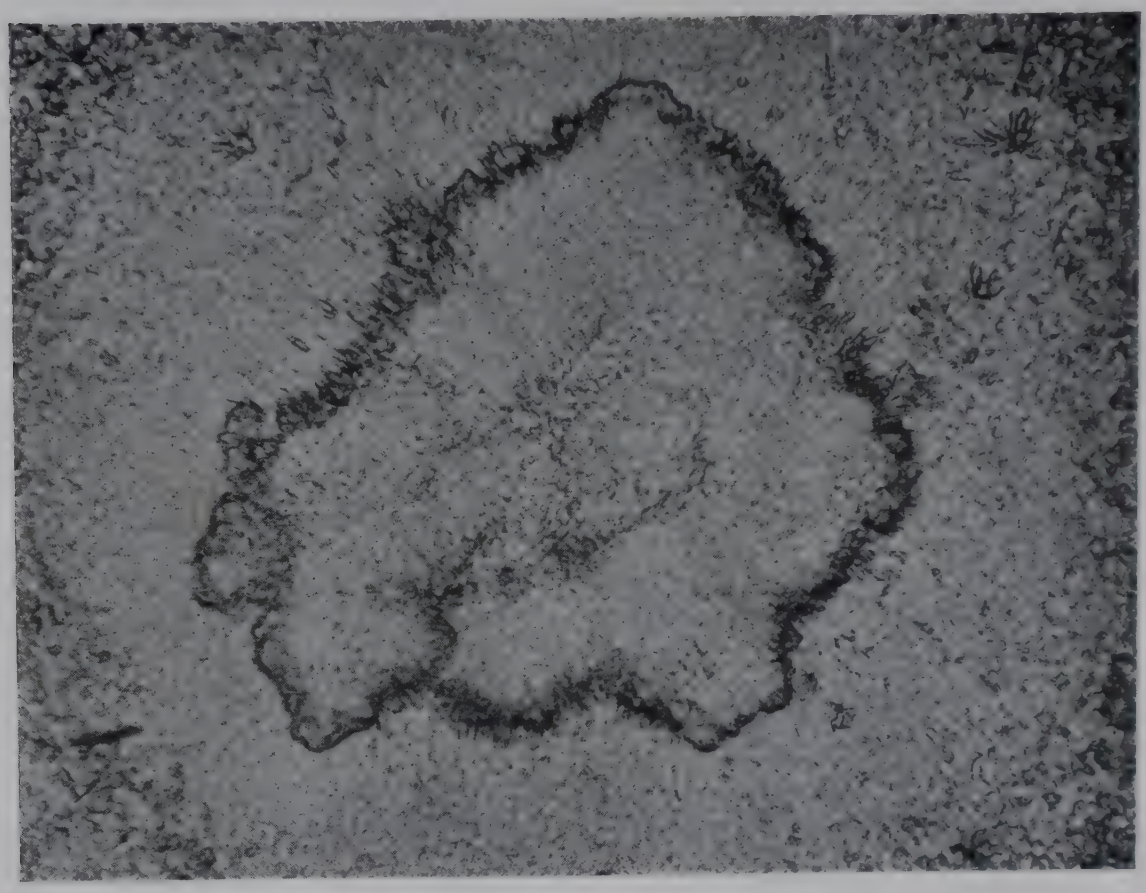

FIG. 117. SULFUR GRANULE IN PUS. × 450

(Courtesy of Conant et al.: Manual of Clinical Mycology, W. B. Saunders Co., 1944; Page 11, Fig. 7 A)

as small granules, hyaline to sulfur yellow in color, made up of a tangled mass of mycelium with a lobulated border that may or may not have radially arranged "clubs." When crushed between two slides, the granules break up into short branching mycelial elements that are gram-positive when stained. In sputum or spinal fluid, organized granules may not be found; but especially in the presence of tuberculosis-like lesions, and

when acid-fast bacilli are absent, gram-positive branching hyphae should be suspected as suggesting Actinomyces.

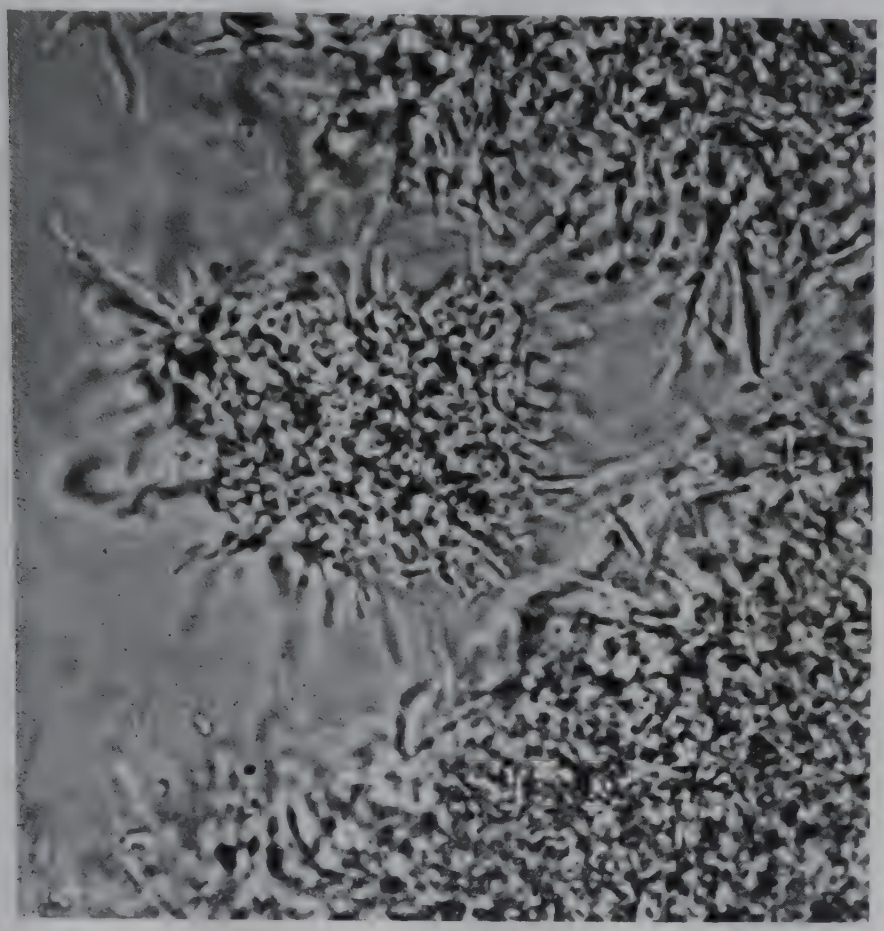

FIG. 118. ACTINOMYCES BOVIS. × 850 (FROM DEEP SHAKE TUBE IN CULTURE)
(Courtesy of Conant et al.: Manual of Clinical Mycology, W. B. Saunders Co., 1944; Page 14, Fig. 9B)

On deep meat infusion agar, incubated at 37 C., the culture will produce colonies in three or four days. These appear as small white fuzzy or lobulated growths, from 3 to 4 mm. below the surface of the agar. Deeper in the tube may be seen large white loculated colonies. Transplants may grow aerobically.

Microscopic examination of a culture mount does not disclose any characteristic structures. The only findings are interlacing hyphae.

Actinomyces (Nocardia) asteroides. The colonies on Sabouraud's glucose agar slants grown at room temperature or at

37 C. show a surface growth which is glabrous, irregularly folded and vary in color from pale yellow to deep orange.

Actinomyces (Nocardia) gypsoides. The colonies on Sa-

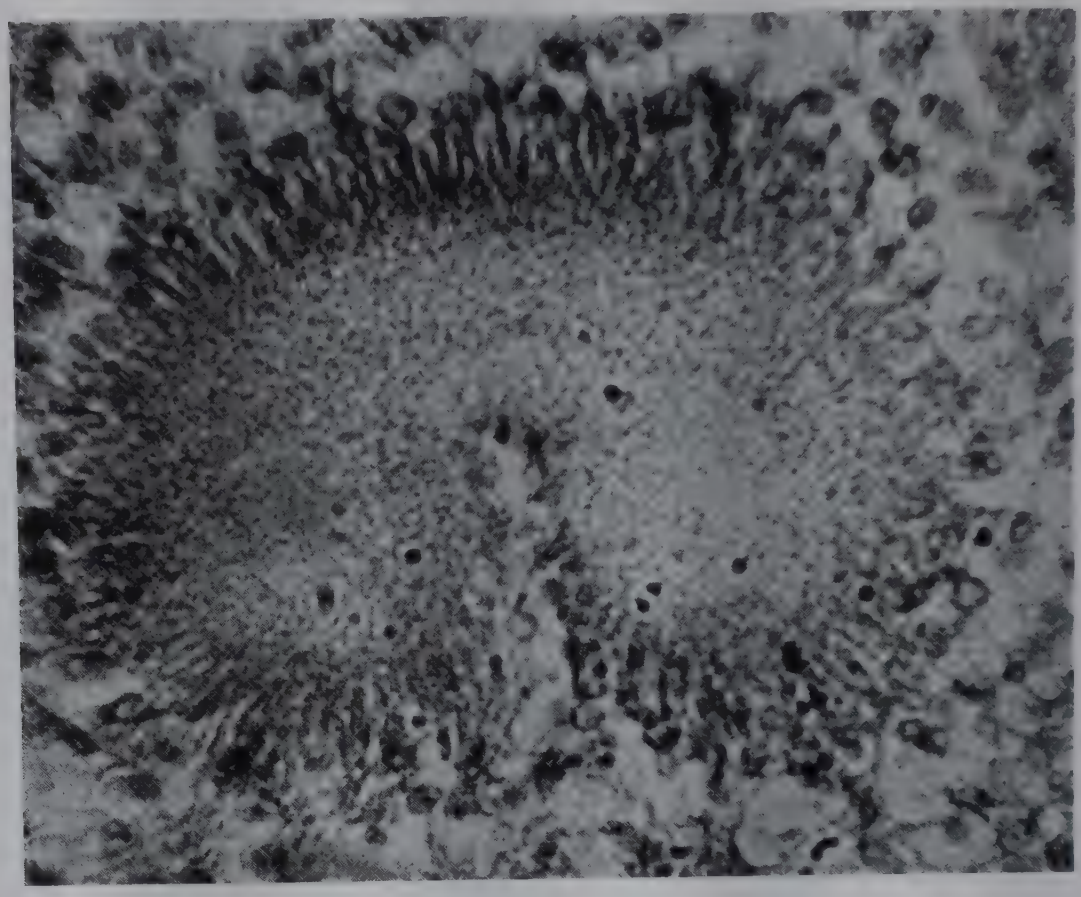

FIG. 119. ACTINOMYCOSIS
Causal organism (ray fungus) in tissue

bouraud's glucose agar slants grown at room temperature or at 37 C. are chalky white.

Actinomyces (Nocardia) madurae. The colonies grown aerobically on Sabouraud's glucose agar at room temperature or at 37 C. show a glabrous, waxy, wrinkled, cream-colored colony. With age, the colonies appear pinkish to varying shades of red.

The microscopic examination of a culture mount of any of the above species of Nocardia shows delicate branching lyphae.

FIG. 120. ACTINOMYCOSIS
(Courtesy of N. F. Conant)

IMMUNOLOGIC REACTION

Agglutination reactions are usually positive but scarcely practical. Cutaneous hypersensitivity to vaccine in patients with the infection has been reported.

CLINICAL MANIFESTATIONS

Almost no tissue or organ escapes. According to Sanford and Voelker, 60 per cent of cases occurring in this country show involvement of the head and neck; 18 per cent are abdominal; 14 per cent are thoracic; 8 per cent show involvement of other organs, including the cutaneous and subcutaneous tissues. The infection may spread by extension or by way of the blood stream.

The clinical manifestations are (1) cutaneous, and (2) visceral.

Cutaneous Manifestations. Although sometimes primary, cutaneous involvement is as a rule secondary to a more deep-seated process. In head and neck involvement, the primary lesion may often be found in the buccal mucous membrane. The gums, the tonsillar crypts or other parts of the mouth may be involved. The initial sign of *primary* cutaneous involvement is usually a solitary nodule in the epidermic layers, the corium and subcutaneous layers showing invasion next by extension. The nodules enlarge gradually, soften, and finally rupture. The discharge is serous, purulent, or sanguineous and contains the characteristic sulfur yellow granules. The primary nodule, after breaking down, forms an ulcer and either heals spontaneously, leaving an atrophic pigmented scar, or continues as a crusted discharging lesion. New nodules develop adjacent to the primary nodule and eventually coalesce, each passing through the same development as did the primary lesion.

The lesions of *secondary* cutaneous involvement are primarily subcutaneous, involving the cutaneous tissue by extension upward. They take the form of deep-seated nodules or tumors of varying sizes, fairly firm to the touch and of a livid hue. They soon break down and develop multiple intercommunicating sinuses that discharge a seropurulent or sanguineopurulent fluid containing the characteristic sulfur yellow granules. The

surrounding skin is usually infiltrated and boardlike to the touch.

Actinomycosis of the cutaneous and subcutaneous tissue may be confused with syphilitic gumma, tuberculosis, coccidioidal granuloma, sporotrichosis, and carcinoma. The differential

Fig. 121. Actinomycosis

points distinguishing actinomycosis are: multiple abscesses, discharging sulfur granules, sinuses, and fistulas with or without fungating granulation tissue masses surrounded by a boardlike induration.

Visceral Manifestations. The various forms are as follows:

Lingual actinomycosis is rare in man, more commonly affecting cattle, hogs, and other domestic animals. In man it may

be primary or secondary to involvement of the buccal or pharyngeal cavities. The first sign is a small deep-seated nodule in the body of the tongue. This enlarges, softens, and finally ruptures, discharging pus that contains the typical sulfur granules. New nodules form elsewhere in the tongue or neighboring on the initial nodule and undergo the same pro-

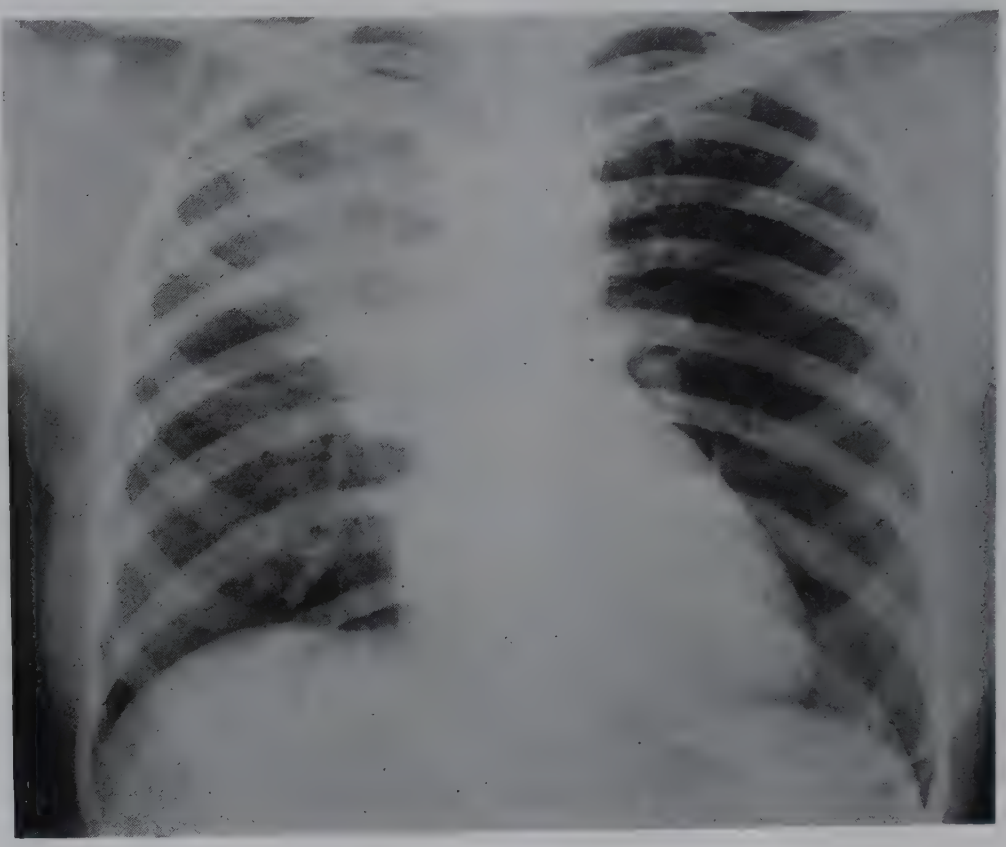

FIG. 122. PULMONARY ACTINOMYCOSIS
(Courtesy of L. L. Robbins)

gressive changes. At first no discomfort is present; with enlargement of the nodule, however, the mucous membrane overlying it is stretched, and the pain thus caused is not relieved until the abscess ruptures.

Pulmonary actinomycosis is rarely primary; most cases are

due to extension or infection by way of the blood stream. There is no characteristic clinical picture on the basis of which diagnosis can be made. A helpful indication is involvement of the bases of the lungs as shown on roentgenologic examination.

FIG. 123. ACTINOMYCOSIS OF CHEST WALL BEFORE TAPPING
(Courtesy of L. L. Robbins)

X-ray examination shows smooth, irregular, massive areas of consolidation without cavity formation, most often in the lower lobes and usually bilateral. In advanced cases the pleura may show either massive adhesions or massive accumulation of fluid which may or may not be encapsulated. The ribs may show both destructive and proliferative changes.

FIG. 124. ACTINOMYCOSIS OF CHEST WALL AFTER TAPPING
(Courtesy of L. L. Robbins)

The most important diagnostic criterion is the presence of the ray fungi in the sputum.

Intestinal actinomycosis is characteristically found, when primary, in the region of the cecum and appendix. Depending on the onset, the course may be chronic or acute. In the latter instance, the picture may simulate acute appendicitis. The chronic form of the infection sometimes becomes extensive, involving many of the abdominal organs before diagnosis is made. Extension of the process through Scarpa's triangle and into the hip joint has been known to occur. The female repro-

ductive organs may also be invaded. In urinary tract infection, the symptoms simulate those of pyelonephritis, cystitis, hypernephroma, carcinoma, or sarcoma. In most of these cases, diagnosis is not established until surgical exploration or autopsy is made.

Cerebrospinal involvement is rare and fatal. The picture may simulate that of meningococcus or tuberculous meningitis.

Osseous involvement is the rarest form of ray fungus infection in man. In cattle, on the other hand, it is common. In the few recorded cases of osseous involvement in man, the bones invaded were those of the vertebral column.

TREATMENT

The response to treatment, even in the most auspicious cases, is slow. The choice of treatment should depend upon the location, type, duration, extent, and severity of the lesion. For the primary cutaneous type the administration of sulfonamide or penicillin supplemented by one or a combination of the old mainstays mentioned below is usually sufficient. For the extensive cases and the systemic type, combined therapy using sulfadiazine, penicillin, plus the old mainstays such as irradiation give the best results. In all extensive and systemic cases, general hygienic measures, a high-calorie and high-vitamin intake, bed rest, iron and liver extract are essential.

Penicillin 50,000 units is administered intramuscularly every three hours, to a total of at least 6,000,000 units. In cases of central nervous system involvement, well-diluted penicillin can be given intrathecally (50,000 units daily).

Sulfadiazine. There is ample evidence that the sulfonamides are useful agents in the treatment of this disease. Sulfadiazine is recommended because of its low toxicity. The initial dose is 2 Gm. and then 1 Gm. every four hours until the patient appears to be clinically well. For prophylactic reasons, the sulfonamide should be continued in doses of 1 Gm. four times

daily, gradually reduced to 3 Gm. and 2 Gm. daily for a period of several months. If any signs of relapse are noticed, intensive therapy should be resumed. Sodium bicarbonate should be prescribed to be taken simultaneously. The urine and blood should be examined at first once a week for one month and then about once every two weeks.

Roentgen ray therapy is a useful supplementary treatment especially in cases of indolent lesions. Good results have been reported with fractional and intensive therapy, with and without filtration.

Surgery should be postponed until after several doses of sulfonamide or penicillin have been administered wherever practical. Adequate surgical drainage is important. Localized accessible lesions may be completely excised.

Iodides as a supplementary treatment may be given as a saturated solution of potassium iodide starting with 15 drops three times a day orally, and increasing 3 drops daily to the point of tolerance. Tincture of iodine in milk or water, starting with 5 drops three times a day and increasing the dose until symptoms of intolerance develop, is another form of iodine therapy. Sodium iodide may be administered intravenously in 1 Gm. doses, once a day in place of potassium iodide. Ethyl iodide inhalation therapy is of particular value in cases of bronchopulmonary involvement. The initial dose is 1.5 cc. (3 Gm.); this is increased by 0.5 cc. (1 Gm.) per dose until 4 cc. (8 Gm.) is reached. Inhalations are given on two successive days and omitted on the third day. A discussion of contraindications and possible complications will be found in the section on moniliasis, Chapter III, p. 54.

Thymol given locally (10 to 20 per cent solution in olive oil) and systemically (capsules of 1 to 2 Gm. by mouth once a day) has been reported as successfully employed.

Copper sulfate (¼ gr.) given by mouth, or colloidal copper administered intravenously, has been used.

Local treatment by irrigation, with penicillin, a diluted

Lugol's solution, or with 1 per cent gentian violet, has been advocated.

Streptomycin has not been used in enough cases of actinomycosis to evaluate its therapeutic index in this disease. Costigan reports cure of a severe case of actinomycosis within five days after institution of treatment with streptomycin, 250,000 units in 2.5 cc. of sterile water every three hours. The same patient did not respond to iodides, penicillin, and sulfonamides.

Vaccine therapy has been used with some success as a supplement to surgery and to penicillin and sulfonamide treatment. Colebrook recommends both stock and antogenous vaccine, in doses of 5,000,000 to 10,000,000 mycelial fragments at intervals of five days.

NOCARDIOSIS

Actinomycosis caused by certain strains of aerobic actinomycetes is known as *Nocardiosis*. The micro-organisms are better known as Nocardia. The clinical manifestations may be indistinguishable from those found in actinomycosis caused by A. bovis. The Nocardia are partially acid fast, gram positive, and occur as branching forms both in the tissue and in culture.

Trichomycosis Axillaris Actinomyces

The causative micro-organism in trichomycosis axillaris is believed by Castellani to be Actinomyces tenuis. Associated micrococci are responsible for the formation of the various pigments.

Weidman reproduced the disease on the hair of the face and axillae in a monkey by feeding the animal a species of Actinomyces that he isolated from a black hairy tongue. The axillary hairs show the presence of firmly attached yellow, red, or black concretions. The yellow and red varieties are those most frequently found in this part of the country.

Shaving the hairs, and use of the following ointment, which loosens the concretions and acts as a fungicide, are of value.

		Gm. or cc.
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0

℔

Trichosporum Hortai

MYCOLOGY

This micro-organism is the cause of tinea nodosa (Piedra), the black node type. On direct microscopic examination of a severed node, one notes branched and septate hyphae. Asci containing two to eight spores may be seen in such preparations. The colony is glabrous and black and in culture mount one sees chlamydospores and asci.

Trichosporum Giganteum

This fungus is considered responsible for the white node type of tinea nodosa. On direct microscopic examination of a severed node, one sees hyphae and an occasional budding cell. The colony is moist and yellow.

CLINICAL PICTURE

Piedra is a disease characterized by the presence of nodes varying in color from light brown to black. As many as twenty-five nodes may be present on a single hair. In South America, it is seen on the scalps of women, whereas in Europe and Asia the moustache and beard of men are affected.

Treatment. (1) Shaving. This is important and may be all that is necessary to effect a cure. (2) Thorough shampoo, followed by the application of bichloride of mercury solution (1:2,000).

Actinomyces Minutissimus

Synonym: Microsporum minutissimum

Little is known about the cultural properties of this organism because of the difficulty of securing cultures. It causes the disease known as erythrasma.

MYCOLOGY

On direct microscopic examination of the cutaneous scales treated with potassium hydroxide, and using the oil immersion lens, fine threadlike structures can be made out.

CLINICAL MANIFESTATIONS

The eruption is macular and covered with a fine scale. Its color is almost identical with that seen in tinea versicolor, varying from yellowish brown to dull red. The areas of predilection are the axillae and groins. Other folds of the skin may be involved.

TREATMENT

A daily bath, followed by the application of the following ointment, is advised.

		Gm. or cc.
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0
℥		

A 25 per cent solution of sodium hyposulfite may be used instead of the ointment above indicated.

Underclothing must be boiled in addition to being washed.

Treatment should be maintained for at least one week after all signs of activity are gone.

Maduromycetic Fungi

A number of fungi have been described as capable of causing

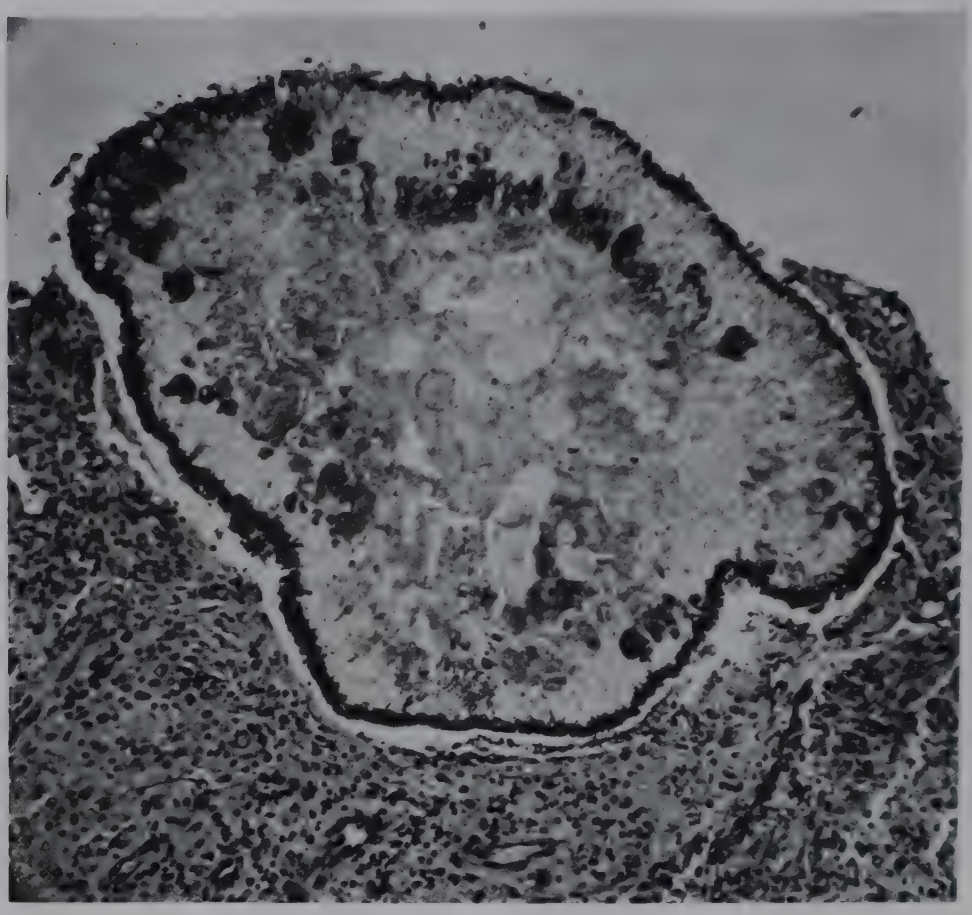

FIG. 125. MADUROMYCOSIS GRANULE IN TISSUE. × 112. MONOSPORIUM APIOSPERMUM CULTURED.

(Courtesy of Smith: Fungus Disease Encountered in General Hospital Practice. Am. J. Med. 3: 602; Fig. 8)

the disease known as mycetoma (maduromycosis). The following are some of the alleged causative micro-organisms, Actinomyces, Madurella, Indiella, Glenospora, Monosporium: Aspergillus, and Penicillium. The disease is endemic in India, especially in the city of Madura, from which the name maduromycosis is derived. It is not common in the United States. All age groups beyond the period of puberty are liable. The disease is more common in males, especially in field hands who habitually go barefoot.

CLINICAL MANIFESTATIONS

The site of infection is the foot, where the initial sign appears

as a subcutaneous swelling that extends to the surface and ruptures, discharging a seropurulent fluid containing yellowish, reddish, or blackish granules. Sinus tracts form, burrowing

FIG. 126. MADUROMYCOSIS OF THE FOOT CAUSED BY MONOSPORIUM APIOSPERMUM
(Courtesy of N. F. Conant)

and extending to the deeper structures, eventually causing malformation. Constitutional symptoms are slight.

TREATMENT

Iodides combined with roentgen ray therapy may be helpful, provided treatment is begun early. Sulfonamides and penicillin are useful in taking care of the usually present superimposed bacterial infection which is frequently the cause of death. These drugs may also be effective if the causal micro-organism is a species of Actinomyces. The dosage and the course of treatment are discussed in the section on actinomycosis, p. 192.

FIG. 127. TINEA VERSICOLOR

In cases where deformity and destruction have already become marked, amputation may be the only recourse.

MALASSEZIA FURFUR

Synonym: Microsporum furfur

This organism has not yet been definitely classified. It is responsible for tinea versicolor (pityriasis versicolor).

MYCOLOGY

On direct microscopic examination of the scales from the

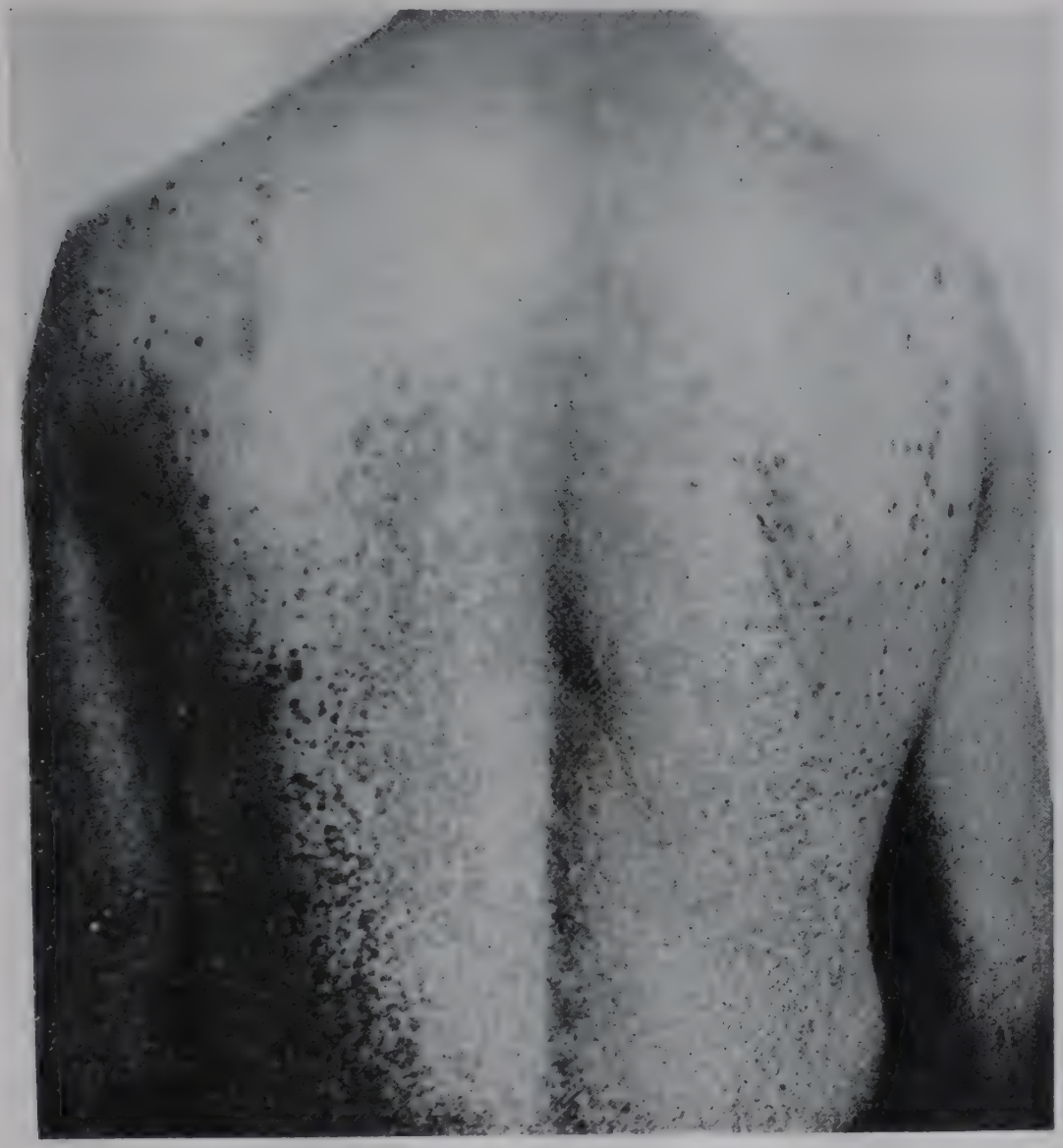

FIG. 128. TINEA VERSICOLOR

lesions, round and budding spores of varying size are seen clustered like bunches of grapes, with usually short and at times curved mycelium. In some preparations the mycelium is the predominating feature; in others, the spores are the most prominent. Routine cultures are not practical since failure to obtain growth is the rule. Moore obtained cultural growth on different media after the initial isolation on maltose broth.

FIG. 129. TINEA VERSICOLOR (ACHROMIA)

CLINICAL MANIFESTATIONS

The eruption in the disease is macular, showing a fine furfuraceous scaling, and is usually a yellowish to dirty brown. The scales vary from pinhead to coin size and may be discrete or coalescent. After exposure to sun, the pigment may be lost and the eruption may have a vitiliginous appearance, retaining the fine scale. The depigmentation can be confused with achromia parasitica, tinea flava, vitiligo, pinta, and syphilitic leukoderma. In rare cases, follicular involvement may be present; the lesions remain small and may become papular. Lesions of tinea versicolor examined under filtered ultraviolet

rays show fluorescence varying from golden yellow to dark brown.

The areas of predilection are the anterior aspects of the

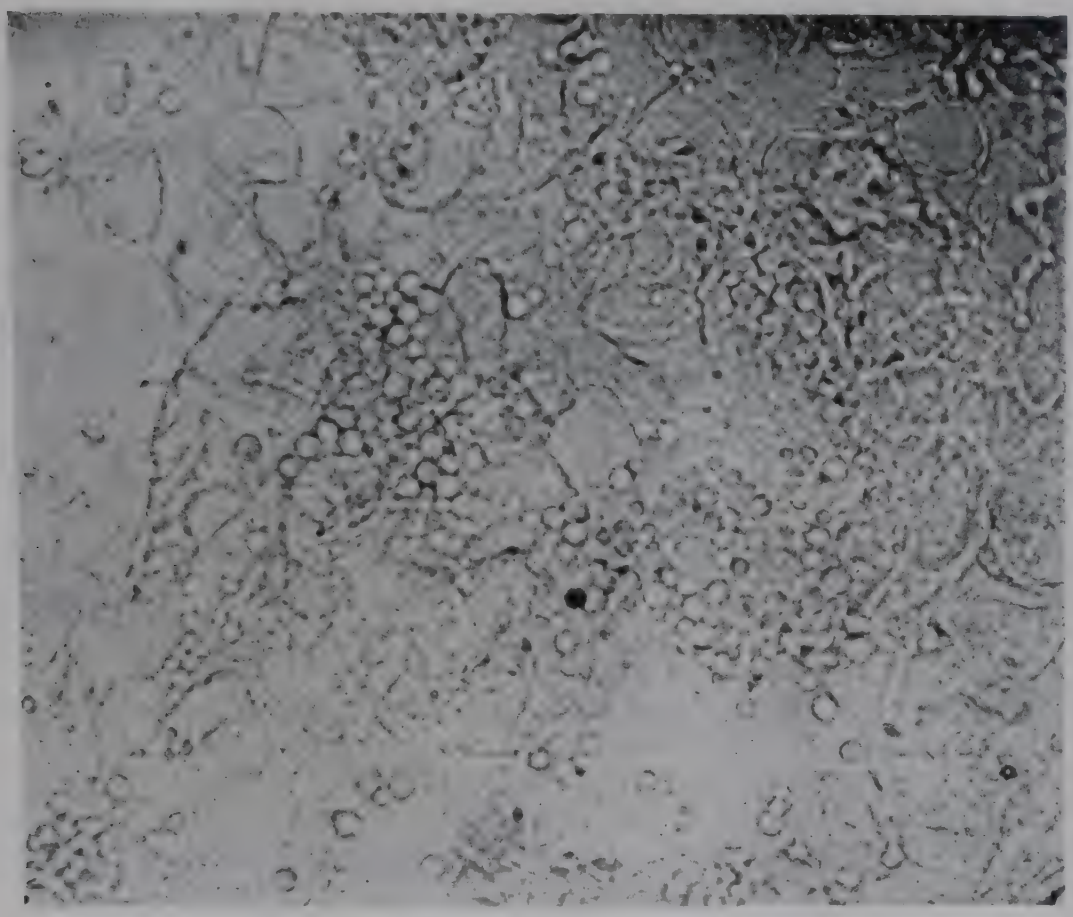

FIG. 130. TINEA VERSICOLOR
Scales showing mycelium and grapelike clusters of fungus spores

thorax, the upper back, and the neck. Occasionally the eruption extends to the abdomen and upper extremities. Cases have been reported in which the axillae and groins have been involved. The eruption is usually asymptomatic and lasts a long time when not treated.

TREATMENT

A hot bath, with scrubbing of the involved parts, followed by the application of sodium hyposulfite solution (25 per cent) or the following ointment, is advised.

		Gm. or cc.
℞	Acidi salicylici	2.0
	Sulphuris praecipitatis	2.0
	Petrolati	30.0

℥

This procedure is to be continued for a week after all clinical signs of the disease have disappeared. The underclothing should be thoroughly washed and boiled, and changed daily.

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CHAPTER VII

COMMON CONTAMINANTS AND PROBABLE PATHOGENS

THE ATMOSPHERE is so filled with common contaminants that they frequently crowd out pathogenic fungi, much to the inconvenience of the laboratory investigator of these organisms. In the laboratory they give even more trouble than the ordinary bacteria, which do not grow well at room temperature.

The common contaminants and probable pathogens include the following:

Aspergillus	Mucor
Penicillium	Hormodendrum
Alternaria	Dematium
Scopulariopsis	Fusarium
Cephalosporium	Torula or Cryptococcus
Mycoderma (Geotrichum)	

Some of these organisms have already been discussed.

ASPERGILLUS

The type species is Aspergillus glaucus. It has a vegetative mycelium made up of septate branching hyphae. These may be hyaline, of bright hue, or, less commonly, brown. The conidia arise from specialized, oversized hyphal cells; the stalks branching from these cells are septate or nonseptate and broaden into ellipsoid, hemispherical, or globose vesicles. The latter show phialides, which may be parallel and clustered in terminal columns or may radiate from the whole surface. The color, shape, and markings of the conidia show wide variety. Septa cut them off successively from the sterigma tips, the conidia being arranged in unbranched chains in a pattern of

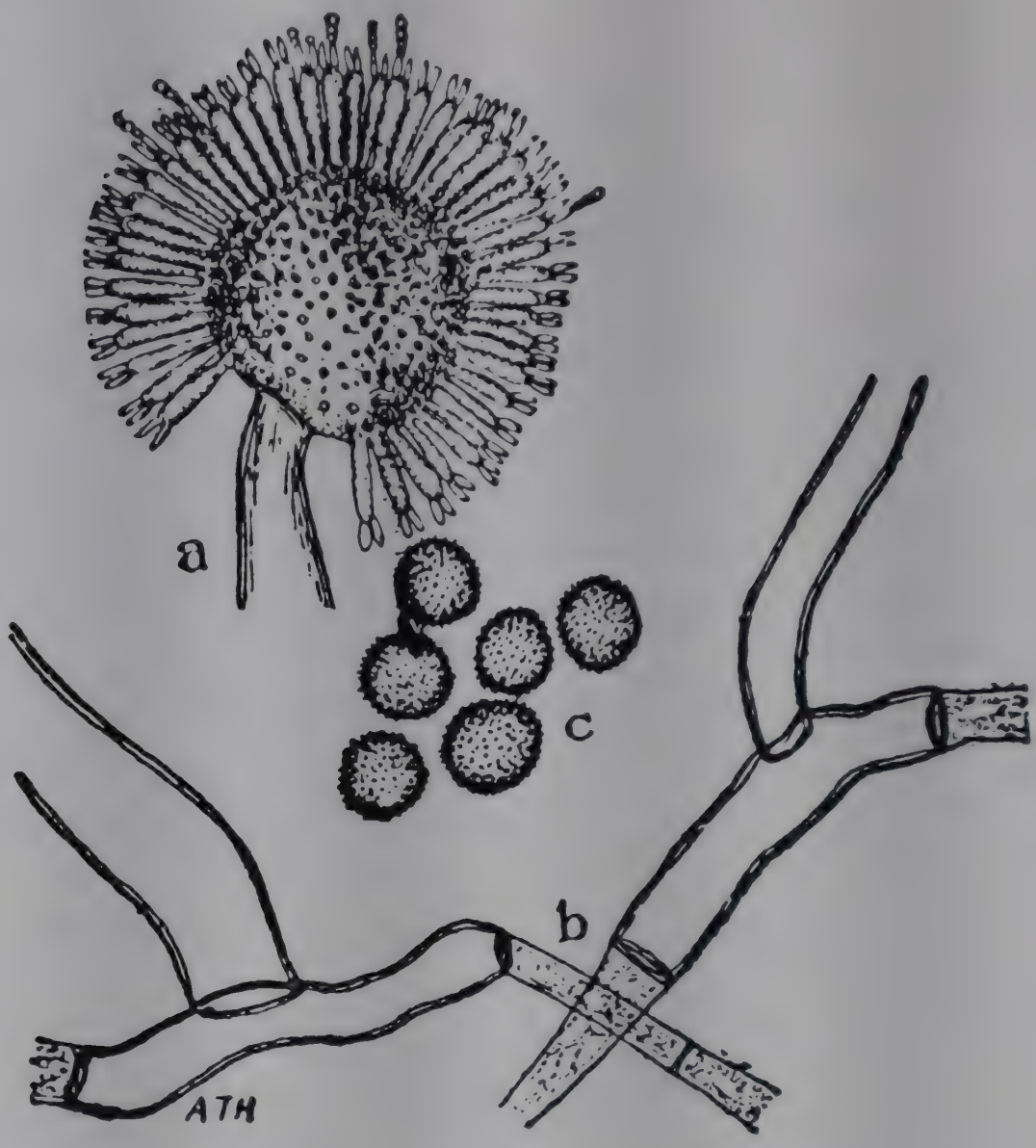

FIG. 131. ASPERGILLUS NIGER

a = spore-bearing head. *b* = mycelium. *c* = spores (Bull. 82, U. S. Department of Agriculture, Bureau of Animal Industry)

radiate heads or in columnar masses. Some species show perithecia that are thin-walled and cleistocarpous, and produce asci and ascospores within a few weeks. Sclerotia, usually spherical or of subspherical shape and made up of thick-walled cells, are characteristically found in some strains while absent in other closely related strains.

A species related to A. nidulans has been found in mycetomas

of the black-grained type. Aspergillus niger and its variants have been blamed for otomycosis, but their pathogenicity is doubtful. Scattered reports in the literature of various species of Aspergillus causing onychomycosis are found. Bereston and Waring report 13 cases. It is not doubted that the unusual can happen, but when Aspergillus is the only micro-organism cultured from the diseased nails, other causes such as systemic diseases must be considered. Pure cultures of Aspergillus, Penicillium, Scopulariopsis, and nonpathogenic yeasts have been grown from diseased nails associated with nutritional disturbances, psoriasis, and other diseases. Even bronchitis and intrinsic asthma have been reported to be due to Aspergillus. Care must be exercised to prove the pathogenicity of the micro-organism by recognized and accepted methods before it is accepted as a direct causative agent. Koch's postulate applies here as elsewhere.

Otomycosis

Various fungi have been blamed for this disease. These include Monilia, Aspergillus, and Penicillium. Aspergillus has been a common finding but autoinoculation experiments by Lewis and Hopper and others have not proved successful. We believe that most cases of so-called otomycosis are caused by bacteria and other agents rather than by fungi. The fungi found are saprophytes living under favorable conditions.

CLINICAL MANIFESTATIONS

Various clinical pictures have been described as otomycosis. The most commonly described findings are swelling and redness of the external ear, a moist mass of cheesy debris completely filling the canal, and exudative skin underlying the debris. The disorder may extend all along the canal and involve the drum. Claims of extension of the infection to the tympanic cavity and the mastoid cell in cases where perforation of the drum is present, have been made. Pruritis is a common and troublesome symptom.

Treatment. In the few proved cases the treatment is directed toward frequent removal of the debris followed by the application of suitable local treatment. A mixture of saturated solution of boric acid, three parts, and alcohol (70 per cent), one part, is used for swabbing involved areas after removal of the debris. This is followed by the application of either a 5 per cent mercurochrome solution or a 1 per cent bacterial fuchsine solution. Metacresyl acetate (cresatin) may be used in place of the mercurochrome or bacterial fuchsine solutions. Roentgen ray treatment in fractional doses may help relieve the pruritis.

Pulmonary Aspergillosis

Of all cases reported only a few were proved. Aspergillus fumigatus and Aspergillus niger were the chief causative species. This infection is more frequent in bird fanciers, grain dealers, and wheat threshers. Pigeons, parrots, and other birds are considered the medium of exposure. A worth-while precautionary measure is the wearing of a gauze mask by grain threshers.

CLINICAL MANIFESTATIONS

Primary infections with Aspergillus are rare. The symptoms are similar to those of pulmonary tuberculosis. Cough is present. The sputum is mucoid or muco-purulent and frequently contains blood. The general health of the patient may not be affected seriously, or there may be remittent fever, loss of weight, obvious toxemia, cachexia, and death. The physical findings are usually indistinguishable from those of chronic pulmonary tuberculosis. Aspergillosis may occur as a secondary infection in tuberculosis, bronchiectasis, and carcinoma of the lungs. Before diagnosis of primary pulmonary aspergillosis is made, other diseases of the lungs must be excluded and cultures of the micro-organism in multiple colonies must be repeatedly demonstrated.

Treatment. Iodide therapy has proved the most effective form of treatment. It must not be administered in cases where pulmonary tuberculosis is suspected. Bed rest, wholesome food, and fresh air are advisable.

Penicillium Link

PENICILLIUM EXPANSUM LINK

Colonies of this organism vary in hue from green to hazel, yellow, red, purple, and other colors. Conidiophores branch from the vegetative mycelium and may be single or branching. The conidia show brush- or broomlike patterning. There is no vesicle. The conidia vary in shape from cylindric to ovoid, ellipsoid, or, in the final form, a spherical conformation. They may be smooth or rough.

Alternaria

The colonies have a dark olive green or brown woolly surface. The spores are large, made up of a number of cells, and multichambered. They appear in chains, sometimes separated by short stretches of mycelium. Most of the species are plant pathogens.

Scopulariopsis

Originally included in the genus Penicillium, this group shows Penicillium-like branching except that it is irregular. The conidiophores may even be unbranched. The terminal branches forming the spores may not show the characteristic apical constriction to a narrow tubular process that is seen in Penicillium. The conidia are large, thick-walled, spiny, and constricted at their bases.

The best known species is Scopulariopsis brevicaulis, which has been reported as having been isolated from lesions of onychomycosis and from gumma-like masses. Its pathogenicity, however, is questionable. Characteristic of it are the pale yellow conidia.

FIG. 132. PENICILLIUM
Conidiophores and conidia, resembling whiskbroom

CEPHALOSPORIUM

CEPHALOSPORIUM ACREMONIUM CORDA

The colony changes from its initial white hue to rose color. The conidiophores are not branched and their tips are not swollen. The conidia arise at the tips, and, though pushed aside

by subsequent conidia, cling together, forming a spherical mass. This species is a common laboratory contaminant.

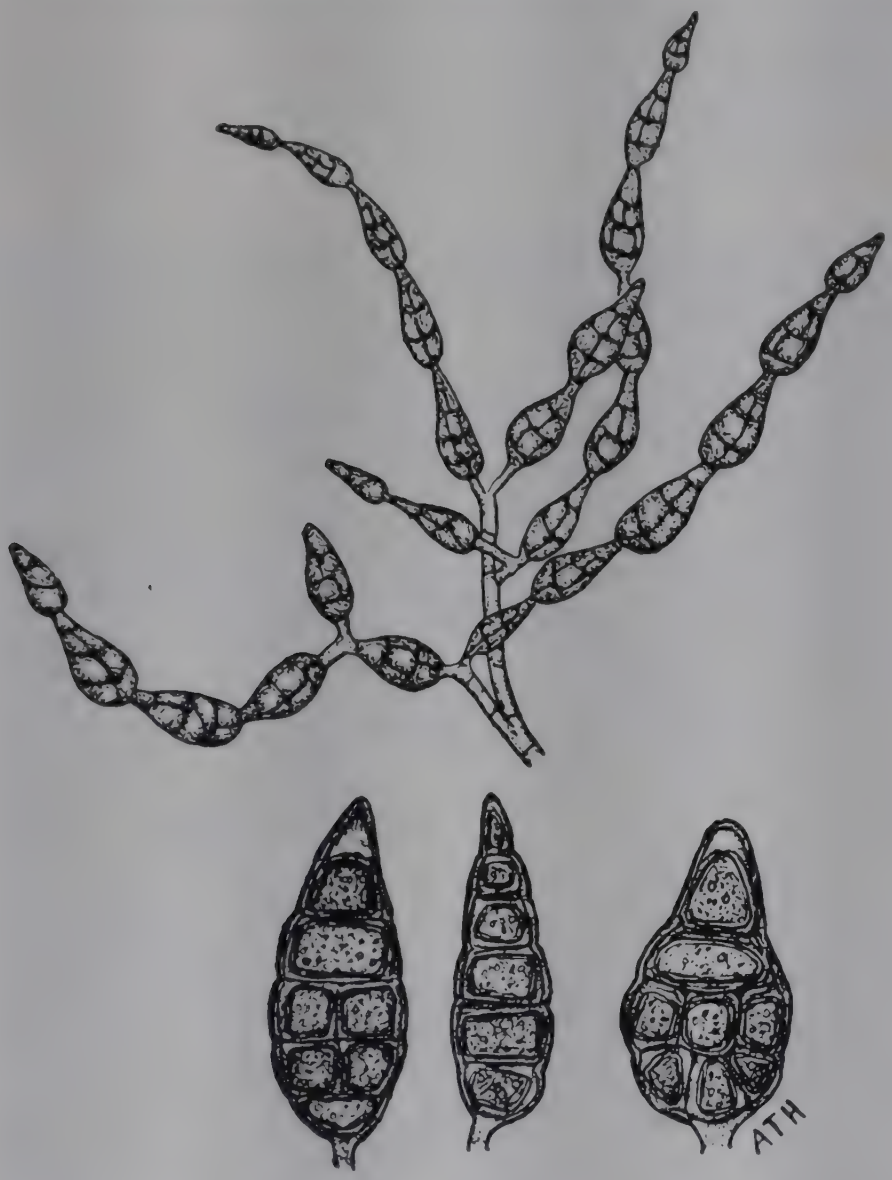

FIG. 133. ALTERNARIA: CHAINS OF FUSEAUX
(Bull. 82, U. S. Department of Agriculture, Bureau of Animal Industry)

GEOTRICHUM LINK

GEOTRICHUM CANDIDUM LINK

The colonies are velvety, dull, membranous, and adhere to the substratum. They form a pellicle on liquid media and liquefy gelatin, but they do not ferment sugars.

Microscopic examination of cultural mounts shows septate mycelium, arthrospores with both abrupt and rounded ends, and small round blastophores. The conidia-like cells are both round and pyriform.

Geotrichum is sometimes classified apart from Mycoderma on the ground that the latter shows more complete gelation of

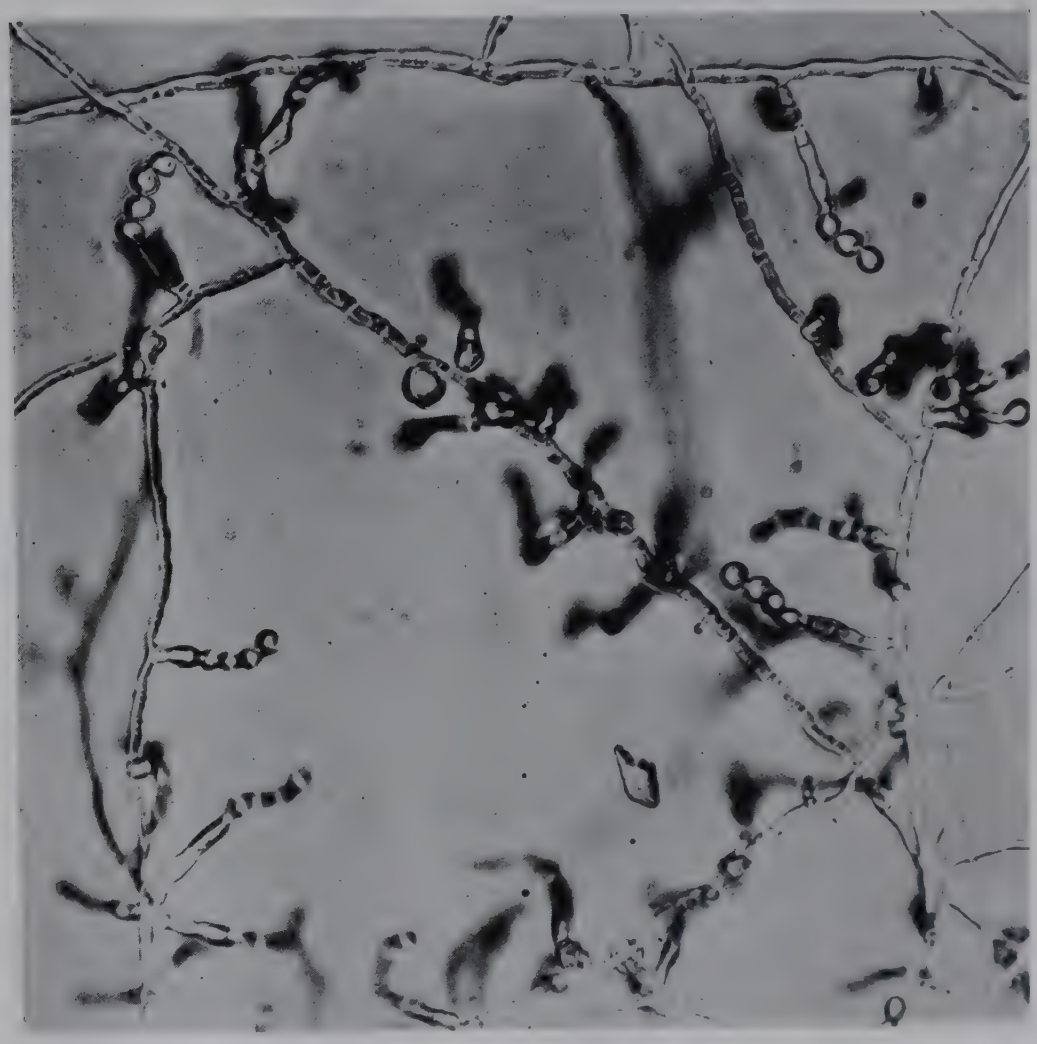

FIG. 134. SCOPULARIOPSIS: MYCELIUM AND CONIDIA

the walls. This is not sufficient reason. The terms should be synonymous and the organisms called Mycoderma should be classified as variants of Geotrichum.

This organism, found in human sputum and excreta, is considered a nonpathogen. It may ultimately prove to be both a

saprophyte and a pathogen. The author has found a high incidence of Geotrichum Link in ulcerative colitis.

This micro-organism has been reported the cause of oral geotrichosis. This infection is characterized by white patches in the mouth, indistinguishable clinically from thrush caused

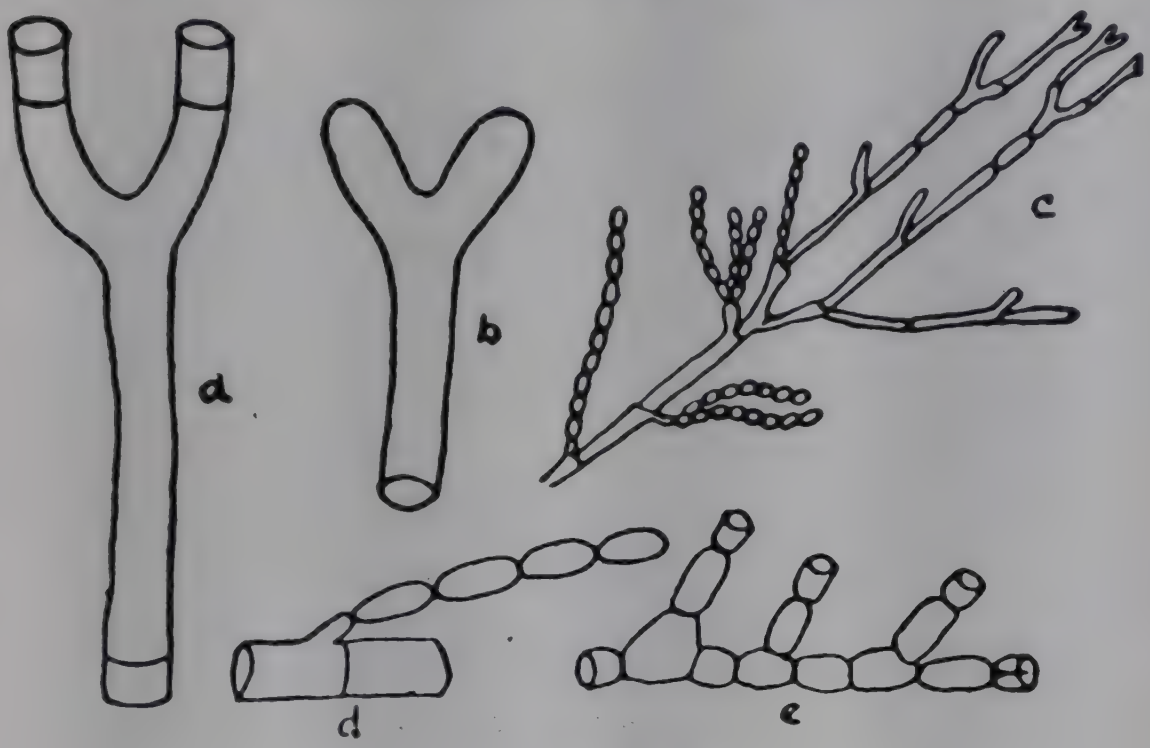

FIG. 135. OIDIUM

a, *b* = dichotomous method of branching. *c*, *d*, *e* = chains of spores
(Bull. 82, U. S. Department of Agriculture, Bureau of Animal Industry)

by candida albicans. Bronchial and pulmonary geotrichosis have been reported. Except for the repeated cultivation of the micro-organism from the sputum one cannot clinically differentiate pulmonary geotrichosis from other diseases of the lung. Like pulmonary aspergillosis this condition may be superimposed upon other pulmonary diseases.

Iodide therapy is effective in all forms of geotrichosis. The method of administration is the same as that described for the treatment of moniliasis. Rest in bed and a high vitamin intake

are essential. Oral geotrichosis may be treated with sodium perborate (3 drachms to ½ glass water) as a mouth wash. Gentian violet, 0.5 to 1 per cent aqueous solution painted on the involved areas, may prove effective.

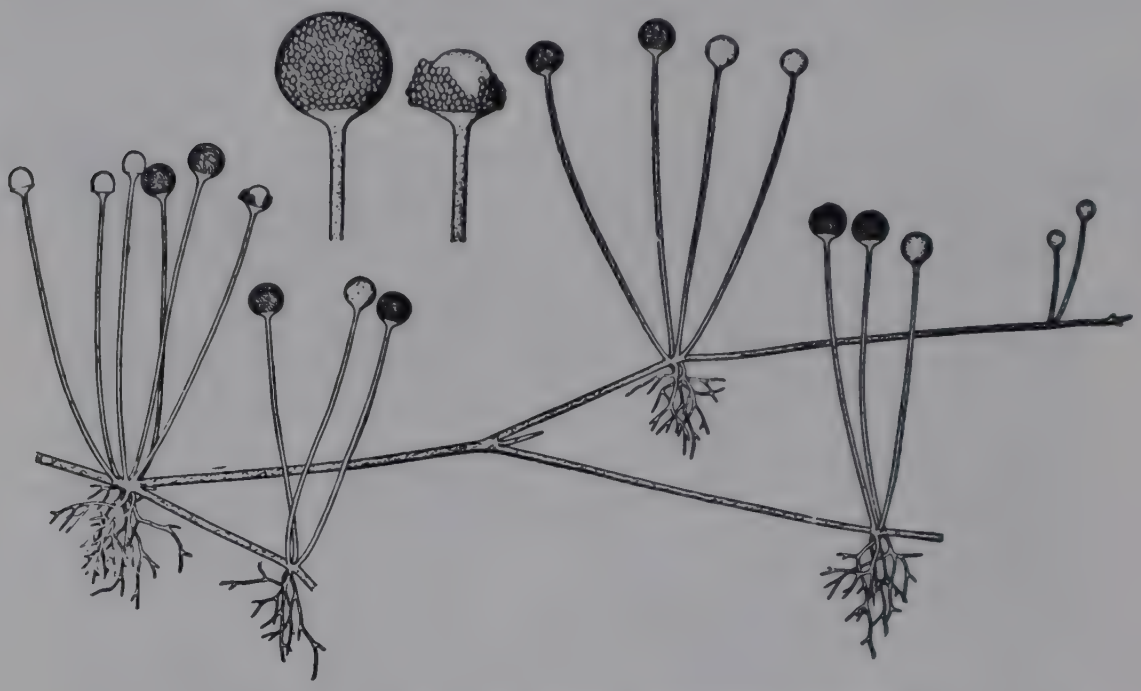

Fig. 136. Rhyzopus Nigricans (Bread Mold)
(Bull. 82, U. S. Department of Agriculture, Bureau of Animal Industry)

Mucor

This is one of the members of the family Mucoraceae. These are a group of molds, frequently referred to as the bread mold, and belonging to the order Phycomycetes. They are also found abundantly in soil, manure, fruits, and starchy foods. The mycelium is coarse and nonseptate. Sporangiophores may be single or show branching. In contrast to the white or gray mycelium, the spores are usually black or brown. The columella is either round, cylindric, or pear-shaped. The sporangium is borne apically on the sporangiophore and its branches.

Hormodendrum and Cladosporium

These molds are widespread, especially on decaying leaves. Colonies have a velvety olive green or brown surface and are almost black on the reverse side. The spores are so arranged

that in a chain the one farthest from the conidiophore is the youngest. This affords a sharp contrast to the spore arrangement in Aspergillus and Penicillium, in which the terminal spore in a chain is the oldest. In Hormodendrum a spore may develop more than one new spore simultaneously, thus causing the chains of conidia themselves to branch.

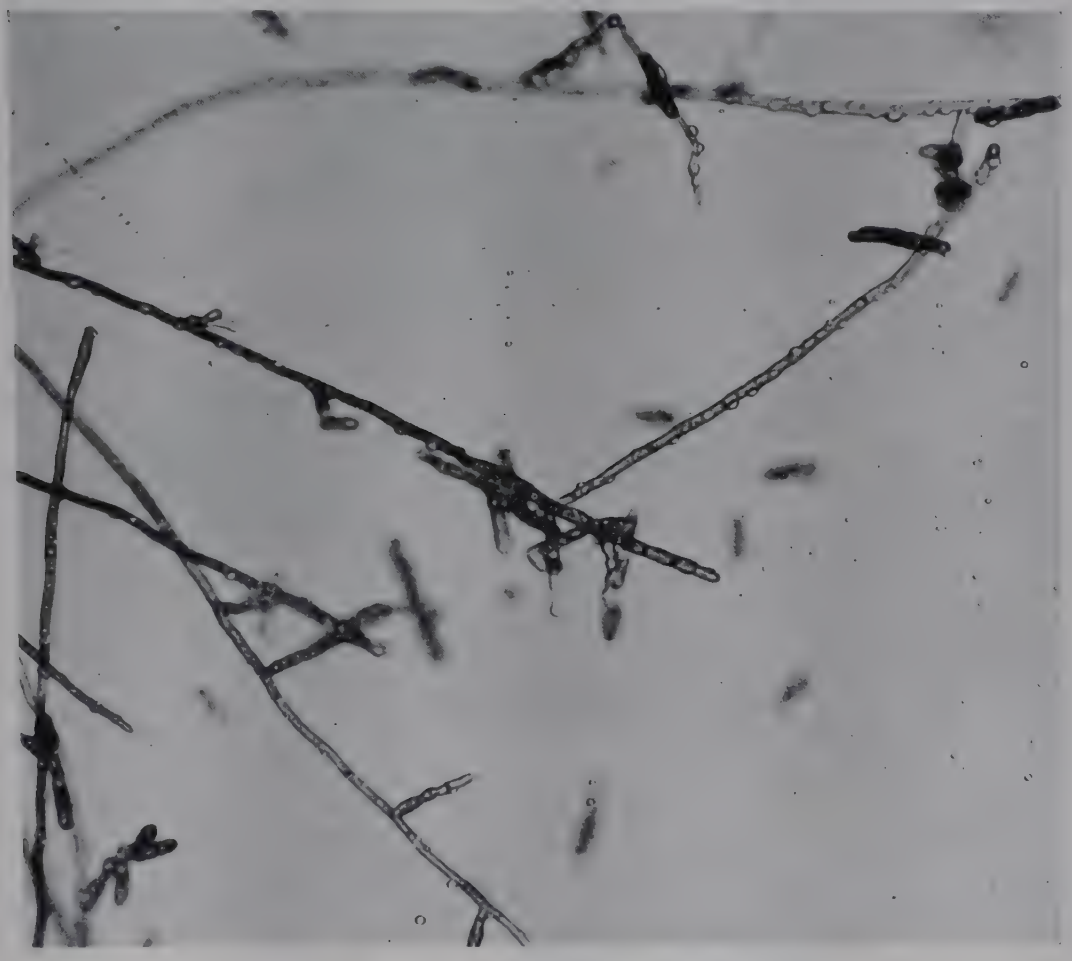

FIG. 137. HORMODENDRUM

DEMATIUM

DEMATIUM ARTICULATUM PERSOON

This species is parasitic or saprophytic on plants. The hyphae are septate and branched, with chains of smooth black arthrospores on lateral branches.

Fusarium

This group contains a large number of plant pathogens and saprophytes. The mycelium is septate and branched. The spores are spindle-shaped. Chlamydospores are present.

Fig. 138. Chaetomium: Spiny Perithecia

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CHAPTER VIII

IMMUNE REACTIONS

Cutaneous sensitization to a fungus, shortly following infection, occurs, but not invariably. The sensitization, as in the case of tuberculosis, may remain for a long time, and therefore the demonstration of the presence of such cutaneous sensitization cannot be regarded as unqualifyingly diagnostic of the skin manifestations. The eruption that may be caused by sensitization to a fungus or to its products is termed dermatophytid.

The Trichophytin Test

Neisser and Plato in 1902 produced an extract of fungi isolated from patients with ringworm. They named this fungus extract trichophytin.

Bloch inoculated animals with Achorion quinckeanum and Trichophyton gypseum and demonstrated that these inoculated animals not only recovered spontaneously but that they also remained immune for as long as a year and a half. Furthermore, all these inoculated animals exhibited a hypersensitiveness to inoculation with trichophytin. Bruhns and Alexander, as well as Fuhs, further found that fungi that produced deep-seated lesions had a greater power to immunize than those that produced superficial lesions. Moreover, it was found that the same fungus could produce a deep infection in one animal and a superficial infection in another. In such instances immunity was produced in the former but not in the latter.

Bloch studied the nature of the trichophytin test in the following manner. He sensitized himself to trichophytin by inoculation with a fungus. A piece of his skin and a piece of skin from another person who was not sensitized to trichophytin were used to cover an ulcer of the leg in a third person not

hypersensitive to trichophytin. Later, trichophytin tests produced a reaction in the skin taken from Bloch but not in the skin of the recipient nor in that of the other donor. This proved the sensitivity of the skin cell itself as a basis for the immune reaction.

Bruch and Kusunoki showed that repeated injections of trichophytin resulted in a weakening of the reaction at the site of inoculation. This was confirmed by Wise and Sulzberger.

Jadassohn and Peck noted that patients with dermatophytids regularly manifested immune reactions to trichophytin. Sulzberger and Lewis reported eczematous reactions to patch testing with trichophytin.

The diagnostic value of the trichophytin test is still questionable for the following reasons. Some of the fungi, such as T. rubrum (T. purpureum) and A. schoenleini, have a low sensitizing index and a negative test therefore does not rule out infection. The test denotes sensitization to a dermatophyte that may have taken place previously, but does not exactly prove that the present eruption is related to the positive reaction obtained. It is, however, a valuable laboratory procedure in conjunction with the clinical and mycologic studies.

The Oidiomycin Test

Oidiomycin is a commercial vaccine made from Monilia albicans. The author's experience of the diagnostic value of this test coincides with the reports of Lewis, Hopper, and Montgomery, of Biberstein and Epstein, and of Staehelin and other workers. This test has been found to be of no value as a diagnostic agent. Too many patients with no evidence of moniliasis showed immune reactions to this test.

Coccidioidin Test

Coccidioidin is prepared from a two months' culture of C. immitis grown at 37 C.

The test consists of the intradermic injection of 0.1 cc. of a 1:100 dilution of a standardized coccidioidin. An erythematous area 0.5 cm. in diameter is considered positive, although this does not necessarily mean activity at the present time. This test is highly specific.

Blastomycin Test

This test is done by the intradermic injection of 0.1 cc. of a standardized Blastomyces vaccine of 1:1,000 dilution. In patients with an active systemic infection the test may be negative.

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CHAPTER IX

ANTIBIOTICS AND NEWER CHEMOTHERAPEUTIC AGENTS

THE KNOWN antibiotics and chemotherapeutic agents have proved to be of little or no value in the treatment of superficial mycoses. Weidman and Chambers noted some inhibitory effect on the superficial mycoses by Bacillus subtilis. Lewis and Hopper using a filtrate of Bacillus (subtilis) X G have demonstrated a potent fungistatic power and feel that it has shown promise of clinical value in the treatment of the superficial mycoses. Tolmach and Lowenthal, and Hopkins and his co-workers feel that clavacin might be useful as a fungistatic agent. Other antibiotics are being studied in the various laboratories including the laboratory of one of the authors (J. H. S.).

The terms "fungistatic" and "fungicidal" must not be used interchangeably. Fungistatic means varying degrees of inhibition of fungus growth. "Fungicidal" means killing of the fungus. Most preparations available for the treatment of fungus infection partially inhibit the growth of the fungus and are therefore fungistatic agents. The mode of action is still debatable because so little is known about the chemistry of the pathogenic fungi, particularly the chemistry of the outer coat or capsule. The therapeutic results obtained in the superficial mycotic infections with our present armamentarium are probably due to the removal of the horny structure harboring the organism either by epilation as in tinea capitis or by keratolytic action as in glabrous skin involvement.

Good results in the treatment of mycotic infection can be obtained either by immune reaction developed by the host or by direct destruction of the fungus with chemicals that are not

injurious to the host. We believe that the reason for failure to accomplish good therapeutic results is the lack of understanding of the chemical structure of the outer coat or capsule of the fungus. One can compare the outer capsule to a bulletproof vest. Until we can penetrate the bulletproof vest, our efforts will be in vain.

Studies for fungistatic and fungicidal properties should include in vivo tests as supplementary studies to in vitro tests. The fungus may be structurally and chemically different on artificial media as compared with the fungus present in the host. This may explain the comparatively poor results obtained in vivo with a proved fungistatic or fungicidal agent by in vitro test.

The actinomyces species is sensitive to some of the newer chemotherapeutic agents because this group of fungi is more closely related chemically and structurally to bacteria than the dermatophytes and the yeastlike fungi.

Some of the antibiotics and newer chemotherapeutic agents have been reported as producing fair to good therapeutic results in some of the deep mycoses. A discussion of the drugs and their therapeutic effects follows.

Sulfonamides

Sulfonamides, preferably sulfadiazine, are effective in the treatment of actinomycosis. Sulfonamides have been employed with good results in some cases of sporotrichosis. In North American blastomycosis, the required concentration in vitro for inhibition of the growth of Blastomyces dermatitidis is well above the maximum clinical drug levels tolerated. It is therefore not effective if used orally or parenterally. Curtis and Grekin report 2 proved cases of histoplasmosis treated with sulfadiazine. Balina et al. reported arrest of the disease in one case of muco-cutaneous involvement. There are still controversial reports on the fungistatic and fungicidal effects of the sulfonamides on Cryptococcus neoformans in vitro.

Keeney et al. found this organism not very susceptible to the sulfonamides, but did obtain complete inhibition of growth in vitro with very high concentrations. Conant et al., Marshall and Teed report improvement with the clinical trial of the sulfonamides in cryptococcosis.

Penicillin

Penicillin has proved effective in the treatment of actinomycosis. Large doses are indicated (see section on Actinomycosis). Hendrickson and Lehman recommend that the penicillin be administered partly by the continuous intravenous-drip method and partly by intramuscular injection. In cases of central nervous system involvement, well diluted penicillin can be given intrathecally. Penicillin has not produced good therapeutic results in sporotrichosis, coccidioidomycosis, moniliasis, blastomycosis (North American), histoplasmosis, and cryptococcosis. However, Meyer has reported that cultures of Cryptococcus neoformans are killed in vitro by penicillin. Hobby and his associates have also found that Cryptococcus neoformans is sensitive to penicillin in vitro. These findings are not confirmed by Keeney and other workers who found that penicillin does not inhibit the growth of Cryptococcus neoformans in vitro.

Streptomycin

There are scattered reports in the literature on the use of streptomycin in actinomycosis but not enough for one to evaluate its therapeutic index. Costigan reports cure of a severe case of actinomycosis within five days after treatment with streptomycin was instituted. The dose was 250,000 units in 2.5 cc. of sterile water every three hours. Streptomycin has not produced good therapeutic results in sporotrichosis and moniliasis. Blastomyces dermatitidis is rather resistant to streptomycin.

Gliotoxin

According to Meyer and Ordal gliotoxin showed a fungistatic action in vitro on Blastomyces dermatitidis but was extremely toxic to the chick embryo.

Table 5.—*Therapeutic Value of Antibiotics and Chemotherapeutic Agents in the Deep Mycoses*

	Sulfonamides	Penicillin	Streptomycin
Actinomycosis	effective	effective	not enough case reports to evaluate
Sporotrichosis	scattered favorable reports	not effective	not effective
Blastomycosis (North American)	not effective	not effective	not effective
Coccidioidomycosis	not effective	not effective	not effective
Moniliasis	not effective	not effective	not effective
Cryptococcosis	controversial reports	not effective	not enough case reports to evaluate
Histoplasmosis	questionably effective	not effective	not enough case reports to evaluate

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GLOSSARY

ABERRANT. Differing from a given species or genus in some respects but not easily assignable to another species or genus

ABJUNCTION. Formation of septae by the cutting off of spores on portions of growing hyphae

ABORTIVE. Not perfect in development

ABSTRICTION. *See* Abjunction

ACHROMATIC. Without color

AERIAL. Living above the surface of ground or water

AEROBIC. Requiring atmospheric oxygen

AGGLUTINATED. Firmly attached as though glued together

ALEUROSPORE. A simple lateral conidium of dermatophytes

AMORPHOUS. Shapeless

ARTHROSPORES. Structures formed by segmentation of a hypha into a chain of cells at first cuboidal and later rounded

ARTICULATE. Jointed

ASCOGENIC. Producing asci

ASCOMYCETES. Fungi in which the spores are borne in saclike cells called asci

ASCOSPORE. Spores borne in a saclike cell called the ascus

ASCUS. The reproductive cell of the perfect stage of the Ascomycetes, containing ascospores

BASIDIOMYCETES. Fungi in which spores are borne on basidia, usually four to a basidium

BASIDIOSPORES. Exposores on a special type of sporophore known as a basidium

BASIDIUM. A special type of sporophore bearing exospores

BLASTOSPORE. A thallospore that arises by budding from the end or side of the parent cell and that may in turn throw out another bud or a mycelial filament, without becoming detached and without any period of latency. The buds of yeast cells are familiar examples

BUFF. Pale creamy gray to creamy yellow

CEREBRIFORM. Brainlike

CHITIN. A substance, allied to horn, that forms the protective covering of many insects, such as beetles, and that is found also in the cell walls of fungi

CHLAMYDOSPORES. Thallospores formed by the concentration of the protoplasm of a hypha within a swollen portion of the filament, the membrane of which becomes thickened. They are purely resting spores and are closely analogous in function to the spores of bacteria

CIRCUMVALLATE. Surrounded

CLAVATE. Thick toward the base; club-shaped

CLAVIFORM. Club-shaped

COLOR OF THE REVERSE. The color of a culture as seen from the underside of an agar slant or a Petri dish

CONCENTRIC. Forming rings or zones within one another in a series

CONIDIA. Cells of irregular shape and size, borne free and originating asexually from the mycelial threads by a process of budding, septation, or abstriction. They may be pedunculated, nonpedunculated, lateral, or terminal

CONIDIOPHORE. A specialized hypha or sporophore bearing conidia

COPULATION. Union of sexual cells

COTTONY. Having a soft and cotton-like surface

CRUSTACEOUS. Having a crust

CRYPTOGRAMS. Plants reproducing by means of spores, e.g., fungi

DENDRITE. Of a form resembling the branching of a tree

DERMATOPHYTE. A fungus parasite found on the skin of man or other animals

DIMORPHIC. Occurring in two forms

DISK. The central part of a surface

DOWNY. Having a fine hairy appearance

DUVET. A soft, finely matted downy coating

ECTO-. Outside (used as prefix)

ECTOTHRIX. A fungus growing on the outside of a hair

ENDEMIC. Confined to a certain area

ENDO-. Within or inside (used as prefix)

ENDO-ECTOTHRIX. A fungus growing both within and outside of a hair

ENDOGENOUS. Originating from inside

ENDOSPORE. Any spore formed within the membrane of the parent cell

ENDOTHRIX. A fungus growing within a hair

EUMORPHIC. Well formed

EXOGENOUS. Originating from outside

FAVIC. Relating to favus or fungus infection of the scalp

FAVOID. Resembling a honeycomb

FERRUGINEOUS, FERRUGINOUS. Reddish brown; of the color of iron rust

FILAMENT. A threadlike structure, as in mycelia

FISSION. Cell division by splitting, as a process of reproduction

FLOCCOSE. Consisting of or bearing woolly tufts

FLUORESCENCE. The property, possessed by certain organic substances, of emitting light of a certain color upon exposure to ultraviolet and other rays

FRUIT BODY. The part of a fungus that bears the spore-producing organs

FUNGACEOUS. Fungus-like

FUNGUS. A thallophyte characterized by the absence of chlorophyll and by the fact that it subsists upon decayed organic matter. It has a vegetative structure known as a mycelium and a reproductive structure known as a spore

FURFURACEOUS. Scaly; branlike

FUSEAU. A multiseptate, thick-walled spore that may be spindle-shaped as in the genus Microsporum, slender and tapering as in the genus Trichophyton, or club-shaped as in the genus Epidermophyton

GENUS. A classification embracing related species
GLABROUS. Devoid of hair
GLOBOSE. Spherical
GUTTATE. Spotted as if by drops
GYMNO-. Naked or uncovered (used as prefix)
GYRATE. Having convolutions
HABITAT. The locality to which an animal is native, or in which a plant naturally grows
HETEROGENEOUS. Different; unlike
HOLDFASTS. Filamentous thallus extensions varying in shape, whose primary function is anchorage or attachment (Rhizopus)
HOST. The animal in which a parasitic fungus lives
HYPHA. A chain of cylindric or club-shaped cells forming a filament
HYPHOMYCETES. A group of imperfect fungi, reproducing by free conidia, with septate mycelium. This is a large group artificially classified together while we await more knowledge of their life history. Most fungi pathogenic to man belong in this group
IMPERFECT STAGE. The stage in which there is no production of sex spores
INARTICULATE. Void of division
INCRUSTED. Covered with a thin, hard crust
INDIGENOUS. Originating in the given region or country
INSPISSATE. Thickened
INTERCALARY. Growing or developing between apex and base
INTERTRIGINOUS. Due to chafing between two surfaces that are near to each another
INTRACELLULAR. Within a cell
INTRICATE. Interwoven
INVAGINATED. Inclosed in a sheath
LACUNAR. Covered with indentations
LANCEOLATE. Narrow and tapering toward the apex
LATERAL. Attached to one side

MACRO-. Large (used as prefix)
MEGA-. Large (used as prefix)
MICRON. One-thousandth part of a millimeter. A unit of size in microscopic measurement
MIOSIS. Reduction of number of divisions of chromosomes
MORPHOLOGIC. Relating to form and structure
MUCOID. Like mucus or slime
MUCUS. Slime
MULTI-. Many or much (used as prefix)
MULTIFORM. Of various shapes
MULTILOCULAR. Having many chambers or cells
MULTISEPTATE. Having many partitions
MYCELIUM. A mass of hyphae or fungus filaments
MYCOLOGY. The study of fungi
MYCOSIS. Disease produced by fungi in animal tissue
NAKED. Devoid of fibrils, scales, or other covering
NODULAR BODIES. Rounded structures made up of closely intertwined hyphae
OIDIA. Having conidia borne in chains
PARASITE. An organism living upon and deriving nurture from another living organism
PECTINATE. Resembling a comb
PEDUNCULATE. Growing on a stalk
PENICILLIFORM. Resembling a brush or broom
PERFECT STAGE. The stage in which the sex spore is present (the ascus in the case of Ascomycetes, the basidium in the case of Basidiomycetes)
PERITHECIUM. A rounded, oval, or pear-shaped structure within which asci are borne
PHIALIDE. A short spore-bearing structure also known as a sterigma
PLEOMORPHISM. The occurrence of more than one independent stage or form in the life cycle of a species
PLURISEPTATE. Having multiple transverse septa
PROTOPLASM. A complex substance forming the living matter of all vegetable and animal cells and tissues

Pseudo-. False (used as prefix)

Psoriasiform. Simulating the scaly papular eruption of a skin disease known as psoriasis

Punctiform. Like a pin point or dot

Purpureous. Reddish purple

Purulent. Containing pus

Pustules. Blisters containing cloudy purulent fluid

Racquet cells. Club-shaped cells, the clubbed end of one cell being attached to the small end of an adjacent cell

Radiate. To spread from a center

Rugose. Wrinkled; ridged

Sanguineous. Blood-colored; pertaining to blood

Saprophyte. Any vegetable organism that lives on decaying organic matter

Sclerotium. An aggregate of resting bodies of small size, composed of a hardened mass of hyphae, from which fruit bodies may develop

Scutula. The cup-shaped crusts found in favus

Septate. Divided by a crosswall

Sessile. Attached by the base, without any distinct projecting support

Species. A classification ranking next below a genus or subgenus, its members possessing certain distinctive permanent characteristics in common

Spinulose. Having small spines

Spiral hyphae. Simple convoluted hyphae that may take all the forms of a tendril—from a spirillum-like form to a closely set coil

Sporangiophore. A sporophore bearing a sporangium

Sporangium. A spore case

Spore. Any of various reproductive bodies or cells produced by plants

Sporophore. A spore-bearing structure

Sporogenesis. Production of spores

Stellate. Starlike

STERIGMA. A specialized hypha to which spores are attached
STRIAE. Furrows
SUB-. Under (used as prefix)
SUBSTRATE, SUBSTRATUM. The material in or upon which a fungus grows
SULCUS. A groove or furrow
SULFUREOUS. Of a sulfur yellow color
SUPER-, SUPRA-. Above (used as prefix)
SYMBIOSIS. The living together of two different organisms
SYNONYM. An alternative but less approved name of a species or genus
TENACIOUS. Tough
THALLOSPORE. A cell that forms a part of the vegetative portion of a fungus
THALLUS. The entire vegetative portion of a fungus
TRANSLUCENT. Transparent; clear
TRUNCATE. Appearing as though cut short at the tip by a transverse line
TUBERCLE. A wartlike excrescence
UMBILICATE. Having a central navel-like depression
UMBO. A boss or protuberance
VEGETATIVE. Growing or food-absorbing
VERRUCOSE. Warty
VERSICOLOR. Changeable in color or of various colors
VESICLE. A blister
VISCID. Sticky
ZYGOSPORE. A sexual type of spore produced by the fusion of two undifferentiated cells

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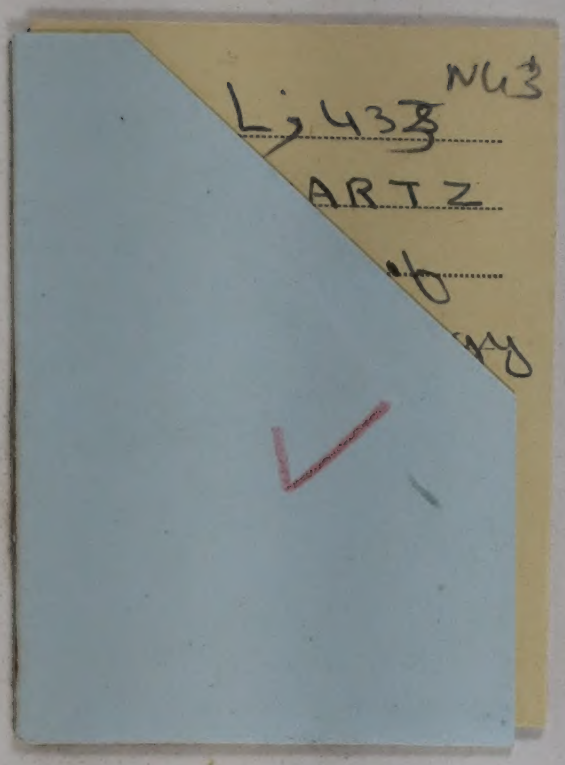
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